number of doses for all dose routes be limited to a total of four. In the USA the recommended schedule for adults undergoing colorectal surgery is metronidazole 15 mg/kg by intravenous infusion over 30 to 60 minutes, completed about 1 hour before surgery, followed by two further intravenous doses of 7.5 mg/kg infused at 6 and 12 hours after the initial dose.

In **peptic ulcer disease**, metronidazole is used in combination therapy to eradicate *Helicobacter pylori*. Typical regimens include metronidazole plus another antibacterial (clarithromycin or amoxicillin) and a proton pump inhibitor. The usual dose of metronidazole is 400 mg twice daily except when given with omeprazole and amoxicillin, when metronidazole 400 mg three times daily is used. Initial treatment is given for 1 week.

For **leg ulcers** and **pressure sores** infected with anaerobic bacteria, oral metronidazole 400 mg may be given three times daily for 7 days. Metronidazole is also applied topically as a 0.75% or 0.8% gel to reduce the odour associated with anaerobic infection in **fungating tumours**.

In the treatment of **rosacea** metronidazole is given orally or applied topically.

General references.

1. Löfmark S, *et al.* Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clin Infect Dis* 2010; **50** (suppl 1): S16–S23.

Administration in children. Metronidazole may be given to children for the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections.

In **invasive intestinal amoebiasis** and **extra-intestinal amoebiasis**, the *BNFC* recommends oral metronidazole, for 5 days for intestinal infection or 5 to 10 days for extra-intestinal infection, in the following doses:

- children aged 1 to 3 years: 200 mg 3 times daily
- those aged 3 to 7 years: 200 mg 4 times daily
- those aged 7 to 10 years: 400 mg 3 times daily
- those more than 10 years: 800 mg 3 times daily

Alternatively experts in the USA[1] recommend oral metronidazole 35 to 50 mg/kg daily in 3 divided doses for 7 to 10 days.

In **giardiasis**, the *BNFC* recommends oral metronidazole in the following doses:

- children aged 1 to 3 years: 500 mg once daily for 3 days
- those aged 3 to 7 years: 600 to 800 mg once daily for 3 days
- those aged 7 to 10 years: 1 g once daily for 3 days
- those aged more than 10 years: 2 g once daily for 3 days, or 400 mg 3 times daily for 5 days, or 500 mg twice daily for 7 to 10 days

Alternatively experts in the USA[1] recommend oral metronidazole 15 mg/kg daily in 3 divided doses for 5 to 7 days.

In **trichomoniasis**, the *BNFC* recommends oral metronidazole in the following doses:

- children aged 1 to 3 years: 50 mg 3 times daily for 7 days
- those aged 3 to 7 years: 100 mg twice daily for 7 days
- those aged 7 to 10 years: 100 mg 3 times daily for 7 days
- those more than 10 years: 200 mg 3 times daily for 7 days or 400 to 500 mg twice daily for 5 to 7 days, or 2 g as a single dose

Alternatively experts in the USA[1] recommend oral metronidazole 15 mg/kg daily in 3 divided doses for 7 days.

For the treatment of most **anaerobic bacterial infections**, the *BNFC* recommends metronidazole is given (usually for 7 days but for 10 to 14 days in antibiotic-associated colitis) in the following doses:

- neonates: 7.5 mg/kg by intravenous infusion every 12 hours
- children 1 to 2 months of age: 7.5 mg/kg orally every 12 hours, *or* 7.5 mg/kg by intravenous infusion every 12 hours
- children aged 2 months and older: 7.5 mg/kg orally (to a maximum of 400 mg) every 8 hours, *or* 7.5 mg/kg by intravenous infusion (to a maximum of 500 mg) every 8 hours

or alternatively

- rectal doses may be given 3 times daily for 3 days, then twice daily thereafter in the following doses: children aged 1 month to 1 year may be given 125 mg, those 1 to 5 years, 250 mg, those 5 to 10 years, 500 mg, and those more than 10 years may be given 1 g

Alternative doses recommended by the American Academy of Pediatrics[2] are:

- for neonates aged ≤7 days and weighing ≤2 kg: a loading dose of 15 mg/kg followed by 7.5 mg/kg given intravenously every 24 to 48 hours; a dosing interval of 48 hours is suggested for extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged ≤7 days and weighing >2 kg: 15 mg/kg given intravenously every 24 hours
- for neonates aged 8 to 28 days and weighing ≤2 kg: 15 mg/kg given intravenously every 24 hours; a dosing interval of 48 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 15 mg/kg given intravenously every 12 hours
- children 1 month and older: 30 to 50 mg/kg given orally in 3 divided doses (to a maximum daily dose of 0.75 to 2.25 g) *or* 22.5 to 40 mg/kg given intravenously in 3 divided doses (to a maximum daily dose of 1.5 g)

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter,2013.
2. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in hepatic impairment. Since metronidazole is mainly metabolised by hepatic oxidation, accumulation of metronidazole and its metabolites is likely in patients with severely impaired hepatic function. Metronidazole should therefore be given with caution and at reduced doses to patients with severe hepatic impairment, and especially hepatic encephalopathy when adverse affects of metronidazole can add to the symptoms of the disease. One-third of the usual daily dose may be given once daily in these patients. For patients with lesser degrees of hepatic impairment, pharmacokinetic studies have not produced consistent results (see under Pharmacokinetics, p. 940.2) and no recommendations about dosage reduction have been made in either the UK or US licensed product information.

Administration in renal impairment. The elimination of metronidazole is largely unchanged in patients with renal impairment, although metabolites may accumulate in patients with end-stage renal disease on dialysis (see under Pharmacokinetics, p. 940.2). Dosage reductions are therefore not usually recommended for patients with renal impairment or for those undergoing peritoneal dialysis. However, both metronidazole and its metabolites are removed by haemodialysis, doses need to be given immediately after haemodialysis.

Dracunculiasis. Metronidazole may be beneficial in the management of dracunculiasis (p. 145.1). It provides symptomatic relief and is also thought to weaken the anchorage of the worms within subcutaneous tissue, thus allowing them to be removed more quickly.

Metronidazole has been given in a variety of regimens, including doses of 400 mg three times daily for 5 days,[1] 40 mg/kg daily in three divided doses (to a maximum daily dose of 2.4 g) for 3 days,[2] and 400 mg daily for 10 to 20 days.[3] WHO recommends 25 mg/kg daily for 10 days;[4] a dose of 250 mg three times daily for 10 days has also been recommended.

1. Padonu KO. A controlled trial of metronidazole in the treatment of dracontiasis in Nigeria. *Am J Trop Med Hyg* 1973; **22**: 42–4.
2. Kale OO. A controlled field trial of the treatment of dracontiasis with metronidazole and niridazole. *Ann Trop Med Parasitol* 1974; **68**: 91–5.
3. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57**: 683–9.
4. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 21/04/09)

Hepatic encephalopathy. The treatment of hepatic encephalopathy is discussed on p. 1811.2. It includes the use of an antimicrobial such as metronidazole to reduce the intestinal flora.

Inflammatory bowel disease. Oral metronidazole is used in the treatment of perineal Crohn's disease (see Inflammatory Bowel Disease, p. 1811.3) and may also be used in colonic Crohn's disease, when it has been tried with ciprofloxacin. It has also proved effective for the prevention of postsurgical recurrence. Duration of therapy is usually limited to 3 months.

Metronidazole ointment is being investigated in the management of perianal Crohn's disease.[1]

1. Maeda Y, *et al.* Randomized clinical trial of metronidazole ointment versus placebo in perianal Crohn's disease. *Br J Surg* 2010; **97**: 1340–7.

Metabolic disorders. Children with excesses of methylmalonic[1-3] and propionic[3,4] acid in their blood or urine have shown clinical improvement when given metronidazole, which reduced the excretion of faecal propionate and urinary methylmalonate. Metronidazole is considered to act through its antimicrobial effect on gut anaerobes that are involved in propionate production; such propionate cannot be handled by these children who are deficient in the relevant enzyme.

1. Bain MD, *et al.* Contribution of gut bacterial metabolism to human metabolic disease. *Lancet* 1988; **i**: 1078–9.
2. Koletzko B, *et al.* Antibiotic therapy for improvement of metabolic control in methylmalonic aciduria. *J Pediatr* 1990; **117**: 99–101.
3. Deodato F, *et al.* Methylmalonic and propionic aciduria. *Am J Med Genet C Semin Med Genet* 2006; **142C**: 104–12.
4. Mellon AF, *et al.* Effect of oral antibiotics on intestinal production of propionic acid. *Arch Dis Child* 2000; **82**: 169–72.

Mouth disorders and infections. Ciclosporin-induced gingival hyperplasia resolved in several patients after treatment with metronidazole.[1,2]

Metronidazole is considered to be effective for the treatment of acute necrotising ulcerative gingivitis and is an alternative to penicillin in other dental infections (see Mouth Infections, p. 192.3).

1. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343**: 986.
2. Cecchin E, *et al.* Treatment of cyclosporine-induced gingival hypertrophy. *Ann Intern Med* 1997; **126**: 409–10.

Peptic ulcer disease. The use of metronidazole is well established in regimens for eradicating *Helicobacter pylori* (see Peptic Ulcer Disease, p. 1816.2). However, the emergence of metronidazole-resistant strains of *H. pylori* has been associated with an increased rate of treatment failures with some regimens.[1-4] The *Helicobacter pylori* Antimicrobial Resistance Monitoring Program (HARP) in the USA[5] reported about a 25% metronidazole resistance rate in clinical *H. pylori* isolates collected from December 1998 through 2002. Difficulties arise in assessing metronidazole resistance and in correlating *in-vitro* results with clinical response.[6] In populations in which the incidence of resistance is high, it may become necessary to use alternative regimens,[7] but in other areas, such as the UK, regimens including metronidazole continue to be among the standard alternatives (although the *BNF* recommends that they should not be used for initial treatment in patients who have been given metronidazole for other infections).

1. Buckley MJM, *et al.* Metronidazole resistance reduces efficacy of triple therapy and leads to secondary clarithromycin resistance. *Dig Dis Sci* 1997; **42**: 2111–15.
2. Lerang F, *et al.* Highly effective twice-daily triple therapies for Helicobacter pylori infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? *Am J Gastroenterol* 1997; **92**: 248–53.
3. Misiewicz JJ, *et al.* One week triple therapy for Helicobacter pylori: a multicentre comparative study. *Gut* 1997; **41**: 735–9.
4. van Zanten SV, *et al.* Adding once-daily omeprazole 20 mg to metronidazole/amoxicillin treatment for Helicobacter pylori gastritis: a randomized, double-blind-trial showing the importance of metronidazole resistance. *Am J Gastroenterol* 1998; **93**: 5–10.
5. Duck WM, *et al.* Antimicrobial resistance incidence and risk factors among Helicobacter pylori-infected persons, United States. *Emerg Infect Dis* 2004; **10**: 1088–94.
6. Goddard AF, Logan RPH. Antimicrobial resistance and Helicobacter pylori. *J Antimicrob Chemother* 1996; **37**: 639–43.
7. Fennerty MB. Should we abandon metronidazole containing Helicobacter pylori treatment regimens? The clinical relevance of metronidazole resistance. *Am J Gastroenterol* 1998; **93**: 2–3.

Skin disorders. Metronidazole may be effective in the management of malodorous anaerobic skin infections associated with ulceration (p. 207.1), including *pressure sores* and *fungating tumours*. Both the oral and topical routes have been employed but the evidence in favour of its use is largely anecdotal as few randomised controlled studies have yet been performed.[1,2]

Metronidazole has also been used[3] in the treatment of *rosacea* (p. 1688.3). Oral metronidazole 200 mg twice daily was more effective than placebo[4] and as effective as oral oxytetracycline.[5] Similarly, topical preparations (for example, 0.75% cream, gel, or lotion or 1% cream) have been found to be better than placebo and as effective as oral oxytetracycline.[6,7]

Oral metronidazole has been tried in the management of *lichen planus*.[8]

1. Clark J. Metronidazole gel in managing malodorous fungating wounds. *Br J Nurs* 200211 (suppl): S54–S60.
2. Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy Wound Manage* 2008; **54**: 18–27.
3. Conde JF, *et al.* Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. *J Drugs Dermatol* 2007; **6**: 495–8.
4. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet* 1976; **i**: 1211–12.
5. Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol* 1980; **102**: 443–5.
6. McClellan KJ, Noble S. Topical metronidazole: a review of its use in rosacea. *Am J Clin Dermatol* 2000; **1**: 191–9.
7. Dahl MV, *et al.* Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. *J Am Acad Dermatol* 2001; **45**: 723–30.
8. Rasi A, *et al.* Efficacy of oral metronidazole in treatment of cutaneous and mucosal lichen planus. *J Drugs Dermatol* 2010; **9**: 1186–90.

Surgical infection. Metronidazole and related nitroimidazoles are used in surgical infection prophylaxis (p. 209.1) to reduce the rate of wound infection.

HAEMORRHOIDECTOMY. Prophylactic metronidazole reduced pain after haemorrhoidectomy in a small study.[1]

1. Carapeti EA, *et al.* Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. *Lancet* 1998; **351**: 169–72.

Adverse Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastrointestinal disturbances, especially nausea and an unpleasant metallic taste. Abdominal pain, anorexia, vomiting, and diarrhoea or constipation may also occur. A furred tongue, glossitis, and

stomatitis may be associated with an overgrowth of *Candida*. There have been rare reports of antibiotic-associated colitis associated with metronidazole, although it is also used in the treatment of this condition.

Weakness, dizziness, ataxia, headache, drowsiness, insomnia, hallucinations, and changes in mood or mental state such as depression or confusion have also been reported. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures have been associated with high doses of metronidazole or prolonged treatment.

There have been rare case reports of agranulocytosis, leucopenia, pancytopenia, and thrombocytopenia, often reversible on stopping of the drug; however, fatalities have occurred. Rashes, urticaria, and pruritus occur occasionally and erythema multiforme, angioedema, and anaphylaxis have been reported rarely. Other adverse effects include urethral discomfort and darkening of the urine. Raised liver enzyme values, cholestatic hepatitis, jaundice, and pancreatitis have occasionally been reported. Thrombophlebitis may follow intravenous use of metronidazole. Other very rarely reported adverse effects include myalgia, arthralgia, and transient visual disorders such as diplopia and myopia.

Studies have shown metronidazole to be mutagenic in bacteria and carcinogenic in some *animals*.

Carcinogenicity and mutagenicity. Metronidazole is mutagenic in bacterial assays, and its hydroxy metabolite even more so, but studies of mammalian cells *in vitro* and *in vivo* have not consistently shown a mutagenic effect. Similarly, there is no uniformity in the limited data concerning genotoxicity in humans,[1] and although metronidazole has been classified as a carcinogen in *animals*, the evidence of human carcinogenicity is ambiguous. There was no appreciable increase in the incidence of cancer in a retrospective study of 771 patients given metronidazole for vaginal trichomoniasis,[2] nor in another similar study of 2460 patients.[3] The first study[2] did show an excess of cases of lung cancer, although all 4 were in women who were smokers. Subsequent follow-up[4] to 1984, covering a period of 15 to 25 years, still showed an excess of lung cancer cases even after allowing for smoking status. However, this follow-up also continued to show no significant increase overall in cancer-related morbidity or mortality. Follow-up[5] of the patients from the second study for 11 to 15 years to 1984 also showed no increase in the overall incidence of cancers nor did it confirm any increase in lung cancer.

Risks to the fetus are discussed under Pregnancy in Precautions, p. 939.2.

1. Bendesky A, *et al.* Is metronidazole carcinogenic? *Mutat Res* 2002; 511: 133–44.
2. Beard CM, *et al.* Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 1979; 301: 519–22.
3. Friedman GD. Cancer after metronidazole. *N Engl J Med* 1980; 302: 519.
4. Beard CM, *et al.* Cancer after exposure to metronidazole. *Mayo Clin Proc* 1988; 63: 147–53.
5. Friedman GD, Selby JV. Metronidazole and cancer. *JAMA* 1989; 261: 866.

Effects on the blood. Adverse haematological effects associated with metronidazole therapy include a report of bone marrow aplasia, with leucopenia and markedly reduced erythropoiesis and granulopoiesis,[1] aplastic anaemia,[2] and the haemolytic-uraemic syndrome.[3]

1. White CM, *et al.* Bone marrow aplasia associated with metronidazole. *BMJ* 1980; 280: 647.
2. Raman R, *et al.* Metronidazole induced aplastic anaemia. *Clinician* 1982; 46: 464–8.
3. Powell ER, *et al.* Haemolytic-uraemic syndrome after treatment with metronidazole. *Med J Aust* 1988; 149: 222–3.

Effects on the ears. A review of reports of ototoxicity notified to the Australian Adverse Drug Reactions Advisory Committee revealed cases of deafness associated with the use of metronidazole.[1] Two cases of bilateral moderate to severe sensorineural deafness after taking oral metronidazole have been reported; in both patients hearing recovered gradually after the drug was stopped.[2]

1. Anonymous. Drug-induced ototoxicity. *WHO Drug Inf* 1991; 5: 12.
2. Iqbal SM, *et al.* Metronidazole ototoxicity–report of two cases. *J Laryngol Otol* 1999; 113: 355–7.

Effects on the eyes. Myopia that developed in a patient after 11 days of oral metronidazole for trichomoniasis had resolved 4 days after withdrawal of treatment, but recurred when she resumed treatment.[1]

Optic neuropathies have also occurred.[2,3] In one report, retrobulbar or optic neuritis was seen in 7 patients given oral metronidazole.[2] Dosage varied from 0.75 to 1 g daily and duration of treatment from 7 days to a year. Abnormalities included defects in colour vision, decreased vision, and scotomas. Vision improved on withdrawal of metronidazole, although there was a residual deficit in 2 patients.

1. Grinbaum A, *et al.* Transient myopia following metronidazole treatment for Trichomonas vaginalis. *JAMA* 1992; 267: 511–12.
2. Putnam D, *et al.* Metronidazole and optic neuritis. *Am J Ophthalmol* 1991; 112: 737.
3. McGrath NM, *et al.* Reversible optic neuropathy due to metronidazole. *Clin Experiment Ophthalmol* 2007; 35: 585–6.

Effects on the gastrointestinal tract. *ANTIBIOTIC-ASSOCIATED COLITIS.* Exposure to antibacterials, particularly broad-spectrum antibacterials, is the most significant risk factor for development of antibiotic-associated colitis (AAC). Antibacterials usually used to treat the disease such as vancomycin and metronidazole have also been shown to cause AAC. AAC has been reported after a 4-day prophylactic course of metronidazole, given rectally[1] and after a 7-day course of oral metronidazole[2]; the condition resolved in both cases after treatment with oral vancomycin for 5 to 7 days. A 25-year-old woman developed AAC after a course of vancomycin and metronidazole, both orally, for pelvic inflammatory disease. The condition resolved after treatment with vancomycin given alone.[3] For further reports on AAC caused by vancomycin see under Vancomycin, p. 385.3.

1. Thomson G, *et al.* Pseudomembranous colitis after treatment with metronidazole. *BMJ* 1981; 282: 864–5.
2. Daly JJ, Chowdary KVS. Pseudomembranous colitis secondary to metronidazole. *Dig Dis Sci* 1983; 28: 573–4.
3. Bingley PJ, Harding GM. Clostridium difficile colitis following treatment with metronidazole and vancomycin. *Postgrad Med J* 1987; 63: 993–4.

Effects on the liver. Severely elevated liver enzyme values, consistent with a drug-induced hepatitis, occurred in a patient given metronidazole hydrochloride 500 mg every 6 hours intravenously for 4 days. He was also receiving cefapirin sodium and tobramycin sulfate.[1] A case of reversible hepatotoxicity caused by an overdose of metronidazole 12.5 g has also been reported.[2] Fatal acute fulminant liver failure probably due to metronidazole occurred in a young woman who had also developed jaundice two years earlier after taking metronidazole.[3]

1. Appleby DH, Vogtland HD. Suspected metronidazole toxicity. *Clin Pharm* 1983; 2: 373–4.
2. Lam S, Bank S. Hepatotoxicity caused by metronidazole overdose. *Ann Intern Med* 1995; 122: 803.
3. Björnsson E, *et al.* Metronidazol as a probable cause of severe liver injury. *Hepatogastroenterology* 2002; 49: 252–4.

Effects on the lungs. Report of a patient who had haemoptysis after ornidazole treatment for lambliasis;[1] he had also had dyspnoea and haemoptysis after similar treatment with metronidazole 10 months previously. Bronchoscopy findings were consistent with diffuse alveolar haemorrhage.

1. Uyar M, *et al.* Diffuse alveolar haemorrhage due to 5-nitroimidazole treatment. *Respirology* 2009; 14: 612–13.

Effects on the nervous system. *ASEPTIC MENINGITIS.* A 42-year-old man had 3 episodes of aseptic meningitis during treatment with oral metronidazole as part of an eradication regimen for *Helicobacter pylori* infection.[1] On each occasion his symptoms resolved spontaneously when eradication treatment was stopped and recurred when treatment was restarted. The aseptic meningitis was attributed to the metronidazole and the patient later tolerated an eradication treatment regimen containing a proton pump inhibitor and a macrolide.

1. Khan S, *et al.* Metronidazole-induced aseptic meningitis during Helicobacter pylori eradication therapy. *Ann Intern Med* 2007; 146: 395–6.

CEREBELLAR TOXICITY. Ataxia and dysarthria have been reported in 2 patients given oral metronidazole plus intravenous cefepime or oral levofloxacin.[1] Symptoms occurred about one month after starting treatment and resolved 2 to 5 weeks after stopping metronidazole. A later report[2] of a patient who developed cerebellar toxicity with objective abnormalities on MRI scanning during metronidazole therapy also identified 10 cases in the literature (including those referred to above). The age range of the patients was 17 to 74 years and most presented with symptoms of ataxia and dysarthria. Cerebellar toxicity in these reports appeared to be related to high cumulative doses of metronidazole (between 25 and 1080 g). Further cases have been reported.[3-5]

1. Woodruff BK, *et al.* Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med* 2002; 346: 68–9.
2. Patel K, *et al.* Cerebellar ataxia following prolonged use of metronidazole: case report and literature review. *Int J Infect Dis* 2008; 12: e111–e114.
3. Graves TD, *et al.* Reversible metronidazole-induced cerebellar toxicity in a multiple transplant recipient. *J Neurol Sci* 2009; 285: 238–40.
4. Sarna JR, *et al.* Cases: reversible cerebellar syndrome caused by metronidazole. *CMAJ* 2009; 181: 611–3.
5. Chatzkel JA, Vossough A. Metronidazole-induced cerebellar toxicity. *Pediatr Radiol* 2010; 40: 1453.

CONVULSIONS. Reports[1-6] of convulsions associated with metronidazole therapy (usually in high doses or in patients with renal impairment).

1. Halloran TJ. Convulsions associated with high cumulative doses of metronidazole. *Drug Intell Clin Pharm* 1982; 16: 409.
2. Wienbren M, *et al.* Convulsions and encephalopathy in a patient with leukemia after treatment with metronidazole. *J Clin Pathol* 1985; 38: 1076.
3. Ferroir JP, *et al.* Polynévrite, crises convulsives et syndrome cérébelleux complications d'un traitement par le métronidazole. *Presse Med* 1985; 14: 2108.
4. Moulin B, *et al.* Risque neurotoxique du métronidazole (MN) au cours de l'insuffisance rénale sévère. *Ann Med Interne (Paris)* 1988; 139: 369.
5. Sopena B, *et al.* Convulsiones inducidas por la asociación de metronidazol y cloroquina. *Med Clin (Barc)* 1990; 95: 675.
6. Beloosesky Y, *et al.* Convulsions induced by metronidazole treatment for Clostridium difficile-associated disease in chronic renal failure. *Am J Med Sci* 2000; 319: 338–9.

EFFECTS ON MENTAL FUNCTION. Although metronidazole is sometimes used to reduce colonic flora in the treatment of hepatic encephalopathy, impaired metabolism of metronidazole in such patients can result in elevated plasma concentrations and consequent toxicity. Psychosis and manic behaviour were reported in a patient during treatment for hepatic encephalopathy with metronidazole and lactulose, although plasma-metronidazole concentrations were not found to be raised (24 micrograms/mL).[1] Symptoms resolved when metronidazole was stopped. Acute psychosis has also been reported in a patient after a 5-day course of intravenous metronidazole 1 g daily for a gynaecological disorder[2] and in an 18- year-old woman after 2 days of [oral] treatment for pelvic inflammatory disease with metronidazole 400 mg three times daily and ofloxacin 400 mg twice daily.[3] In another patient who developed probable metronidazole-associated encephalopathy after taking oral metronidazole, the symptoms gradually resolved over a period of 2 to 4 months.[4] Hallucinations[5] and confusion[5,6] have also been reported in other patients without hepatic encephalopathy; in undernourished patients it has been suggested that metronidazole-induced encephalopathy might involve a common pathway with Wernicke's encephalopathy,[7] from which it must be distinguished. Irreversible metronidazole-associated encephalopathy leading to death has been reported in a patient given 1.5 g as a single intravenous dose daily over 10 weeks as part of a regimen to treat osteomyelitis.[8] It has been suggested[9] that patients taking metronidazole for prolonged durations may be at increased risk of encephalopathy.

1. Uhl MD, Riely CA. Metronidazole in treating portosystemic encephalopathy. *Ann Intern Med* 1996; 124: 455.
2. Schreiber W, Spernal J. Metronidazole-induced psychotic disorder. *Am J Psychiatry* 1997; 154: 1170–1.
3. Koul S, *et al.* Organic psychosis induced by ofloxacin and metronidazole. *Br J Hosp Med* 2009; 70: 236–7.
4. Khodakaram K, Barmano N. Uncommon reaction to a common prescription. *Lancet* 2011; 378: 288.
5. Mahl TC, Ummadi S. Metronidazole and mental confusion. *J Clin Gastroenterol* 2003; 36: 373–4.
6. Kim DW, *et al.* Metronidazole-induced encephalopathy. *J Neurol Sci* 2004; 224: 107–11.
7. Zuccoli G, *et al.* Metronidazole-induced and Wernicke encephalopathy: two different entities sharing the same metabolic pathway? *AJNR Am J Neuroradiol* 2008; 29: E84.
8. Groothoff MV, *et al.* Irreversible encephalopathy after treatment with high-dose intravenous metronidazole. *Clin Ther* 2010; 32: 60–4.
9. Bottenberg MM, *et al.* Metronidazole-induced encephalopathy: a case report and review of the literature. *J Clin Pharmacol* 2011; 51: 112–6.

PERIPHERAL NEUROPATHY. Peripheral neuropathy has been reported in patients given metronidazole, usually for long periods.[1-7] Stopping metronidazole or lowering the dose usually results in complete resolution or improvement of the neuropathy but in some patients it may persist despite these measures. For reports of retrobulbar or optic neuritis associated with metronidazole, see Effects on the Eyes, above.

1. Duffy LF, *et al.* Peripheral neuropathy in Crohn's disease patients treated with metronidazole. *Gastroenterology* 1985; 88: 681–4.
2. Boyce EG, *et al.* Persistent metronidazole-induced peripheral neuropathy. *DICP Ann Pharmacother* 1990; 24: 19–21.
3. Learned-Coughlin S. Peripheral neuropathy induced by metronidazole. *Ann Pharmacother* 1994; 28: 536.
4. Dreger LM, *et al.* Intermittent-dose metronidazole-induced peripheral neuropathy. *Ann Pharmacother* 1998; 32: 267–8.
5. Zivkovic SA, *et al.* Sensory neuropathy associated with metronidazole: report of four cases and review of the literature. *J Clin Neuromusc Dis* 2001; 3: 8–12.
6. Sarma GRK, Kamath V. Acute painful peripheral neuropathy due to metronidazole. *Neurol India* 2005; 53: 372–3.
7. Toumi S, *et al.* Lésions cérébelleuses réversibles et neuropathie périphérique induites par le métronidazole. *Med Mal Infect* 2009; 39: 906–8.

Effects on the pancreas. A small number of cases of acute pancreatitis associated with metronidazole, in some cases recurrent on rechallenge, have been reported.[1-8] The delay between metronidazole exposure and the onset of pancreatitis ranged from 12 hours to 38 days. All cases of pancreatitis were moderate and resolved after stopping the metronidazole. No cases were found in a retrospective study of about 6500 patients given metronidazole.[9] However, another retrospective analysis[10] of 3083 patients found that metronidazole may increase the risk of acute pancreatitis, but mainly when it is used with other drugs for the eradication of *Helicobacter pylori*.

1. Plotnick BH, *et al.* Metronidazole-induced pancreatitis. *Ann Intern Med* 1985; 103: 891–2.
2. Sanford KA, *et al.* Metronidazole-associated pancreatitis. *Ann Intern Med* 1988; 109: 756–7.
3. Sura ME, *et al.* Metronidazole-associated pancreatitis. *Ann Pharmacother* 2000; 34: 1152–5.

4. Tsesmeli NE, *et al.* Acute pancreatitis as a possible consequence of metronidazole during a relapse of ulcerative colitis. *Eur J Gastroenterol Hepatol* 2007; 19: 805–6.
5. Feola DJ, Thornton AC. Metronidazole-induced pancreatitis in a patient with recurrent vaginal trichomoniasis. *Pharmacotherapy* 2002; 22: 1508–10.
6. Nigwekar SU, Casey KJ. Metronidazole-induced pancreatitis. A case report and review of literature. *JOP* 2004; 5: 516–9.
7. Loulergue P, Mir O. Metronidazole-induced pancreatitis during HIV infection. *AIDS* 2008; 22: 545–6.
8. O'Halloran E, *et al.* Metronidazole-induced pancreatitis. *HPB Surg* 2010; 2010: 523468.
9. Friedman G, Selby JV. How often does metronidazole induce pancreatitis? *Gastroenterology* 1990; 98: 1702–3.
10. Nørgaard M, *et al.* Metronidazole and risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2005; 21: 415–20.

Gynaecomastia. Gynaecomastia occurred in a 36-year-old man with ulcerative colitis after taking metronidazole for about a month.[1]

1. Fagan TC, *et al.* Metronidazole-induced gynecomastia. *JAMA* 1985; 254: 3217.

Hypersensitivity. A hypersensitivity reaction with chills, fever, generalised erythema, and a maculopapular rash developed after a single oral dose of metronidazole in a patient who had previously developed a rash during treatment with intravaginal metronidazole.[1] There have been a few case reports of fixed drug eruptions with oral metronidazole[2,3] and ornidazole[4] with cross-sensitivity to other nitroimidazoles (but not necessarily all of them); provocation or patch tests may be done with care to establish cross-sensitivity. Cutaneous exanthemas[5] in patients taking metronidazole have also been reported. Anaphylaxis has been reported,[6,7] including a case after an oral dose of metronidazole and spiramycin in which the subsequent skin prick test was positive for metronidazole.[6] Allergic contact dermatitis has been reported after application of topical metronidazole formulations.[8]

1. Knowles S, *et al.* Metronidazole hypersensitivity. *Ann Pharmacother* 1994; 28: 325–6.
2. Sehgal VN, *et al.* Bullous fixed drug eruption (BFDE) following per-oral metronidazole. *J Eur Acad Dermatol Venereol* 2003; 17: 607–9.
3. Prieto A, *et al.* Recurrent fixed drug eruption due to metronidazole elicited by patch test with tinidazole. *Contact Dermatitis* 2005; 53: 169–70.
4. Sanmukhani J, *et al.* Fixed drug eruption with ornidazole having cross-sensitivity to secnidazole but not to other nitro-imidazole compounds: a case report. *Br J Clin Pharmacol* 2010; 69: 703–4.
5. García-Rubio I, *et al.* Hypersensitivity reactions to metronidazole. *Allergol Immunopathol (Madr)* 2006; 34: 70–2.
6. Asensio Sánchez T, *et al.* Anaphylaxis due to metronidazole with positive skin prick test. *J Investig Allergol Clin Immunol* 2008; 18: 138–9.
7. Schmutz JL, *et al.* Réaction anaphylactique au métronidazole. *Ann Dermatol Venereol* 2009; 136: 759.
8. Madsen JT, *et al.* Allergic contact dermatitis to topical metronidazole - 3 cases. *Contact Dermatitis* 2007; 56: 364–6.

Precautions

Neurotoxic symptoms including peripheral neuropathy and transient epileptiform seizures, and other serious effects such as leucopenia have sometimes been associated with prolonged or intensive treatment with metronidazole (see Adverse Effects, p. 937.3). Clinical and laboratory monitoring is advised in patients given metronidazole for more than 10 days. Metronidazole should be used with caution in patients with blood dyscrasias or CNS disease; it should be stopped in those who develop abnormal neurological signs. Doses should be reduced in patients with severe hepatic impairment.

It is suggested that the use of metronidazole should be avoided during pregnancy, and this caution applies especially to use during the first trimester and to the use of high-dose regimens (see also below).

Patients are advised not to drink alcoholic beverages while taking metronidazole (see under Interactions, below).

Breast feeding. Metronidazole is distributed into breast milk giving it a bitter taste that may impair feeding.[1] The last available guidance from the American Academy of Pediatrics considered that although the effects of metronidazole on breast-fed infants were unknown they might be of concern. It recommended that breast feeding should be stopped for 12 to 24 hours when single-dose therapy was used;[2] no specific recommendations were given for long-term treatment. Unnecessary exposure to metronidazole should be avoided because it has been found to be mutagenic and carcinogenic in some studies (see under Adverse Effects, p. 938.1).

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; 293: 1415–17.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/02/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metronidazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Pregnancy. Metronidazole is mutagenic in bacteria and carcinogenic in *rodents*. It readily crosses the placenta achieving similar concentrations in the placental cord and maternal plasma and its use in pregnancy is controversial. Meta-analyses of studies involving the use of metronidazole in the first trimester of pregnancy[1,2] concluded that there did not appear to be an increased risk of teratogenicity. Furthermore, a small study[3] that reviewed the use of metronidazole in 922 women during pregnancy found no association between metronidazole treatment at any stage of pregnancy and preterm birth, low birth weight, or congenital anomalies.However, in the USA licensed product information considers metronidazole to be contra-indicated during the first trimester in patients with trichomoniasis; use for trichomoniasis during the second and third trimesters may be acceptable. For other indications the risks and benefits of treatment with metronidazole should be weighed carefully, especially in the first trimester. In the UK, the *National Teratology Information Service* notes that the limited available data do not indicate an increased risk to the fetus from maternal use of metronidazole during pregnancy (although high-dose regimens for bacterial vaginosis are not recommended), and recommends that the drug should not be withheld in pregnancy if there is a compelling indication for its use.[4]

1. Burtin P, *et al.* Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995; 172: 525–9.
2. Caro-Patón T, *et al.* Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997; 44: 179–82.
3. Koss CA, *et al.* Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrob Agents Chemother* 2012; 56: 4800–5.
4. National Teratology Information Service. Use of metronidazole in pregnancy (issued October 2012). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Metronidazole%202012.pdf (accessed 12/06/13)

Interactions

When given with alcohol, metronidazole may provoke a disulfiram-like reaction in some patients. Acute psychoses or confusion have been associated with the use of metronidazole and disulfiram together.

Metronidazole is reported to impair the metabolism or excretion of several drugs including coumarins and warfarin (p. 1532.3), phenytoin (p. 544.1), lithium (see Antimicrobials, p. 431.3), ciclosporin, and fluorouracil (p. 797.3), with the consequent potential for an increased incidence of adverse effects. There is some evidence that phenytoin might accelerate the elimination of metronidazole. Plasma concentrations of metronidazole are decreased by phenobarbital, with a consequent reduction in the efficacy of metronidazole. Cimetidine has increased plasma concentrations of metronidazole.

For incompatibilities between metronidazole and other drugs in solutions for injection, see p. 936.2.

Alcohol. Metronidazole may provoke a disulfiram-like reaction in some individuals when given with alcohol; reactions have occurred after the use of preparations formulated with alcohol, including injections, as well as after drinking alcohol.[1] Acute psychosis or confusional state was reported in 6 of 29 alcoholic patients who were also taking disulfiram.[2] However, an analysis of published reports[3] and a study in healthy subjects[4] both found that there was no convincing evidence of a disulfiram-like reaction between metronidazole and alcohol, although caution was still advised.

Licensed product information for some other 5-nitroimidazole derivatives warns of a potential interaction with alcohol but apart from an isolated report for ornidazole[5] there do not appear to be any other published reports to support this.

1. Edwards DL, *et al.* Disulfiram-like reaction associated with intravenous trimethoprim-sulfamethoxazole and metronidazole. *Clin Pharm* 1986; 5: 999–1000.
2. Rothstein E, Clancy DD. Toxicity of disulfiram combined with metronidazole. *N Engl J Med* 1969; 280: 1006–7.
3. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother* 2000; 34: 253–7.
4. Visapää J-P, *et al.* Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother* 2002; 36: 971–4.
5. Sharma V, *et al.* Disulfiram-like reaction with ornidazole. *J Postgrad Med* 2009; 55: 292–3.

Antiepileptics. For a report of a possible interaction between metronidazole and *carbamazepine*, see p. 517.2.

An increase in the rate of metabolism of metronidazole, resulting in treatment failure, was reported in a patient taking *phenobarbital*.[1] In a retrospective survey of patients who had not responded to treatment with metronidazole, 80% were found to be on long-term phenobarbital therapy.[2] Up to 3 times the usual dose was required to produce a parasitological cure of giardiasis in such patients.

In addition to conflicting reports on the effects of metronidazole on the metabolism of *phenytoin* (p. 544.1), increased metabolism of metronidazole was reported in a patient during treatment with phenytoin.[3]

1. Mead PB, *et al.* Possible alteration of metronidazole metabolism by phenobarbital. *N Engl J Med* 1982; 306: 1490.
2. Gupte S. Phenobarbital and metabolism of metronidazole. *N Engl J Med* 1983; 308: 529.
3. Wheeler LA, *et al.* Use of high-pressure liquid chromatography to determine plasma levels of metronidazole and metabolites after intravenous administration. *Antimicrob Agents Chemother* 1978; 13: 205–9.

Antineoplastics. For reference to the effect of metronidazole on *busulfan*, see p. 756.1.

Disulfiram. For a report of acute psychosis or confusional state after metronidazole treatment in alcoholic patients receiving disulfiram, see under Alcohol, above.

Gastrointestinal drugs. In a study in 6 healthy subjects metronidazole plasma concentrations were increased by twice-daily doses of *cimetidine*. The effect was presumed to be due to inhibition of cytochrome P450 isoenzymes responsible for metronidazole metabolism.[1] However, cimetidine was not found to affect the pharmacokinetics of metronidazole in a study in patients with Crohn's disease[2] nor in a single-dose study in healthy subjects.[3]

Although concentrations in plasma and saliva of metronidazole and its hydroxy metabolite were unaffected by *omeprazole* in healthy subjects, those in gastric juice were substantially lowered, possibly as a result of a reduction in transfer from the plasma.[4] However, this may be of limited clinical significance during treatment of *Helicobacter pylori* infections.

1. Gugler R, Jansen JC. Interaction between cimetidine and metronidazole. *N Engl J Med* 1983; 309: 1518–19.
2. Eradiri O, *et al.* Interaction of metronidazole with cimetidine and phenobarbital in Crohn's disease. *Clin Pharmacol Ther* 1987; 41: 235.
3. Loft S, *et al.* Lack of effect of cimetidine on the pharmacokinetics and metabolism of a single oral dose of metronidazole. *Eur J Clin Pharmacol* 1988; 35: 65–8.
4. Jessa MJ, *et al.* The effect of omeprazole on the pharmacokinetics of metronidazole and hydroxymetronidazole in human plasma, saliva and gastric juice. *Br J Clin Pharmacol* 1997; 44: 245–53.

Immunosuppressants. For details of a pharmacokinetic study reporting reduced exposure to *mycophenolate mofetil* when given with metronidazole or metronidazole plus norfloxacin, see Antibacterials, p. 1968.2.

Antimicrobial Action

Metronidazole is active against most anaerobic protozoa including *Balantidium coli, Blastocystis hominis, Entamoeba histolytica, Giardia intestinalis* (*Giardia lamblia*), and *Trichomonas vaginalis*. Anaerobic bacteria which are typically sensitive are Gram-negative anaerobes belonging to the *Bacteroides fragilis* group, *Prevotella* spp., and *Fusobacterium* spp. and Gram-positive anaerobes such as *Peptococcus niger, Peptostreptococcus, Clostridium* spp., and susceptible strains of *Eubacterium*. It is bactericidal. It also has variable activity against the facultative anaerobes *Gardnerella vaginalis* and *Helicobacter pylori*.

Resistance has been reported and about 70 to 75% of *Actinomyces* spp. and *Propionibacterium propionica* are resistant to metronidazole. Cross-resistance to other nitroimidazoles, such as tinidazole, may occur.

Metronidazole is considered to be a prodrug that needs to be activated by susceptible organisms. The mechanism of action is not entirely clear, but is thought to involve reduction by bacterial 'nitroreductases' to an unstable intermediate which interacts with DNA, effectively preventing further replication.[1] Several factors affect the sensitivity of micro-organisms to metronidazole *in vitro*. Anaerobic conditions are important for optimal activity. Interactions between micro-organisms and metronidazole have been described, including inhibition of *Escherichia coli* by metronidazole in the presence of *B. fragilis* and enhancement of the rate of killing of *B. fragilis* by metronidazole in the presence of *E. coli*. The oxidative metabolites of metronidazole also have antibacterial activity; the hydroxy metabolite has been reported to be consistently more active than metronidazole against strains of *G. vaginalis*.[2,3]

Resistance to metronidazole has developed in sensitive species including the *B. fragilis* group,[4-10] other *Bacteroides* spp.[11-13] (now known as *Prevotella* spp.), and rarely to *C. difficile*.[14,15] Metronidazole resistance has also been documented for *T. vaginalis*[16-19] and *Giardia* strains.[19] Nitroimidazole resistance in *Helicobacter pylori* has been increasing and may be associated with reduced response rates to anti-*Helicobacter* therapy for peptic ulcer disease in some populations (see Peptic Ulcer Disease under Uses, p. 937.3).

1. Ingham HR, *et al.* Interactions between micro-organisms and metronidazole. *J Antimicrob Chemother* 1982; 10: 84–7.
2. Ralph ED, Amatmieks YE. Relative susceptibilities of Gardnerella vaginalis (Haemophilus vaginalis), Neisseria gonorrhoeae, and Bac-

teroides fragilis to metronidazole and its two major metabolites. *Sex Transm Dis* 1980; 7: 157–60.
3. Shanker S, Munro R. Sensitivity of Gardnerella vaginalis to metabolites of metronidazole and tinidazole. *Lancet* 1982; i: 167.
4. Ingham HR, *et al.* Bacteroides fragilis resistance to metronidazole after long-term therapy. *Lancet* 1978; i: 214.
5. Eme A, *et al.* Bacteroides fragilis resistant to metronidazole. *J Antimicrob Chemother* 1983; 12: 523–5.
6. Lamothe P, *et al.* Bacteroides fragilis resistant to both metronidazole and imipenem. *J Antimicrob Chemother* 1986; 18: 642–3.
7. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; 23: 660–2.
8. Hickey MM, *et al.* Metronidazole resistant Bacteroides fragilis infection of a prosthetic hip joint. *J Infect* 1990; 20: 129–33.
9. Turner P, *et al.* Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of Bacteroides fragilis. *Lancet* 1995; 345: 1275–7.
10. Schapiro JM, *et al.* Isolation of metronidazole-resistant Bacteroides fragilis carrying the nimA nitroreductase gene from a patient in Washington State. *J Clin Microbiol* 2004; 42: 4127–9.
11. Sprott MS, *et al.* Metronidazole-resistant anaerobes. *Lancet* 1983; i: 1220.
12. McWalter PW, Baird DR. Metronidazole-resistant anaerobes. *Lancet* 1983; i: 1220.
13. Sprott MS, Kearns AM. Metronidazole-resistant Bacteroides melaninogenicus. *J Antimicrob Chemother* 1988; 22: 951–2.
14. Peláez T, *et al.* Reassessment of Clostridium difficile susceptibility to metronidazole and vancomycin. *Antimicrob Agents Chemother* 2002; 46: 1647–50.
15. Brazier JS, *et al.* Reduced susceptibility of Clostridium difficile to metronidazole. *J Antimicrob Chemother* 2001; 48: 741–2.
16. Cudmore SL, *et al.* Treatment of infections caused by metronidazole-resistant Trichomonas vaginalis. *Clin Microbiol Rev* 2004; 17: 783–93.
17. Schwebke JR, Barrientes FJ. Prevalence of Trichomonas vaginalis isolates with resistance to metronidazole and tinidazole. *Antimicrob Agents Chemother* 2006; 50: 4209–10.
18. Crowell AL, *et al.* In vitro metronidazole and tinidazole activities against metronidazole-resistant strains of Trichomonas vaginalis. *Antimicrob Agents Chemother* 2003; 47: 1407–9.
19. Upcroft P, Upcroft JA. Drug targets and mechanisms of resistance in the anaerobic protozoa. *Clin Microbiol Rev* 2001; 14: 150–64.

Pharmacokinetics

Metronidazole is readily and almost completely absorbed after oral doses. Peak plasma concentrations of about 6 and 12 micrograms/mL occur, usually within 1 to 2 hours, after single doses of 250 and 500 mg respectively. Some accumulation occurs and consequently there are higher concentrations when multiple doses are given. Absorption may be delayed, but is not reduced overall by food. Metronidazole benzoate suspension given orally is hydrolysed in the gastrointestinal tract to release metronidazole, which in turn is then absorbed.

Peak steady-state plasma concentrations of about 25 micrograms/mL with trough concentrations of about 18 micrograms/mL have been reported in patients given an intravenous loading dose of 15 mg/kg followed by 7.5 mg/kg every 6 hours. The bioavailability of metronidazole from rectal suppositories is 60 to 80%; peak plasma concentrations are half those achieved with equivalent oral doses and effective concentrations occur after about 5 to 12 hours. Absorption from vaginal pessaries is poor with a reported bioavailability of about 20 to 25%; absorption is gradual producing peak plasma concentrations of about 2 micrograms/mL after a dose of 500 mg. An intravaginal gel formulation providing a dose of 37.5 mg metronidazole produced peak plasma concentrations of 300 nanograms/mL at 8 hours, with a bioavailability of 56%.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast milk, cerebral abscesses, CSF, liver and liver abscesses, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma. It also crosses the placenta and rapidly enters the fetal circulation. No more than 20% is bound to plasma proteins.

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The principal oxidative metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the hydroxy metabolite), which has antibacterial activity and is detected in plasma and urine, and 2-methyl-5-nitroimidazole-1-acetic acid (the acid metabolite), which has virtually no antibacterial activity and is often not detected in plasma, but is excreted in urine. Small amounts of reduced metabolites, acetamide and *N*-(2-hydroxyethyl)oxamic acid (HOA), have also been detected in urine and are probably formed by the intestinal flora.

The elimination half-life of metronidazole is about 8 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates (see below) and in patients with severe hepatic impairment (see below); that of the hydroxy metabolite is prolonged in patients with substantial renal impairment (see below).

The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

References.
1. Cunningham FE, *et al.* Pharmacokinetics of intravaginal metronidazole gel. *J Clin Pharmacol* 1994; 34: 1060–5.
2. Lamp KC, *et al.* Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999; 36: 353–73.

Hepatic impairment. There have been differing results from pharmacokinetic studies of the elimination of metronidazole in patients with hepatic impairment. No marked difference was reported[1] between patients with cirrhosis or hepatosplenic schistosomiasis given a single 500-mg oral dose of metronidazole when compared with healthy subjects; this suggested that, in the absence of renal impairment, dosage adjustment was not needed in patients with hepatic impairment. However, others found[2] that elimination of metronidazole, given intravenously, was considerably impaired in a study of 10 patients with alcoholic liver disease or chronic active hepatitis, 7 of whom also had reduced creatinine clearance. Responding to the comment[3] that these differing results were probably due to impaired renal elimination, the authors suggested[4] that impaired elimination of metronidazole was due to impaired hepatic metabolism rather than decreased renal clearance; other studies have shown metronidazole clearance to be normal in renal impairment. They nevertheless agreed that reduction in the dosage of metronidazole is required only when hepatic function is very poor, particularly when renal function is impaired. A study in 10 severely ill patients with or without impaired hepatic and/or renal function[5] also suggested that hepatic function is a very important determinant of metronidazole elimination.

1. Daneshmend TK, *et al.* Disposition of oral metronidazole in hepatic cirrhosis and in hepatosplenic schistosomiasis. *Gut* 1982; 23: 807–13.
2. Farrell G, *et al.* Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1983; 287: 1845.
3. Daneshmend TK, Roberts CJC. Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984; 288: 405.
4. Farrell G, *et al.* Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984; 288: 1009.
5. Ljungberg B, *et al.* Metronidazole: pharmacokinetic observations in severely ill patients. *J Antimicrob Chemother* 1984; 14: 275–83.

Infants and children. A single intravenous dose of 15 mg/kg has been suggested for neonates,[1] which would produce therapeutic concentrations of metronidazole for about 24 hours in term neonates and 48 hours in preterm neonates. Renal and hepatic function is incompletely developed in newborn infants and consequently the elimination half-life of metronidazole is prolonged and has been reported to range from 25 to 109 hours.[1] Elimination half-life is inversely proportional to gestational age[1,2] and as the infant matures half-life is reduced to values closer to those in adults.[1,3]

1. Jager-Roman E, *et al.* Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr* 1982; 100: 651–4.
2. Hall P, *et al.* Intravenous metronidazole in the newborn. *Arch Dis Child* 1983; 58: 529–31.
3. Amon L *et al.* Disposition kinetics of metronidazole in children. *Eur J Clin Pharmacol* 1983; 24: 113–19.

Renal impairment. Pharmacokinetic studies have indicated that doses of metronidazole need not be altered in patients with renal impairment,[1] although adjustments might be required in patients undergoing haemodialysis, since metronidazole and its hydroxy metabolite are efficiently cleared and extensively removed in such patients.[2] However, in another study[3] the amount of metronidazole and its hydroxy metabolite cleared was found to depend on the type of dialysis membrane used; the authors concluded that dosage supplementation may be needed only for seriously ill patients undergoing haemodialysis with a membrane having high metronidazole clearance.

Routine adjustment of dosage was not considered necessary in patients undergoing peritoneal dialysis.[4] However, the potential for metabolites to accumulate was noted in patients on continuous ambulatory peritoneal dialysis[5] and it was suggested that dosage reduction may be necessary if excessive concentrations of metabolites are found to be toxic.

1. Houghton GW, *et al.* Pharmacokinetics of metronidazole in patients with varying degrees of renal failure. *Br J Clin Pharmacol* 1985; 19: 203–9.
2. Somogyi A, *et al.* Disposition and removal of metronidazole in patients undergoing haemodialysis. *Eur J Clin Pharmacol* 1983; 25: 683–7.
3. Lau AH, *et al.* Hemodialysis clearance of metronidazole and its metabolites. *Antimicrob Agents Chemother* 1986; 29: 235–8.
4. Cassey JG, *et al.* Pharmacokinetics of metronidazole in patients undergoing peritoneal dialysis. *Antimicrob Agents Chemother* 1983; 24: 950–1.
5. Guay DR, *et al.* Pharmacokinetics of metronidazole in patients undergoing continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 1984; 25: 306–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bexon; Colpofilin; Dazotron†; Etronil; Flagyl; Format; Ginkan; Gynotran; Metral; Metrizol; Metrocev; Metrodermic; Metrolocal; Nalox; Ovufem; Padet; Repligen; Rozex; Rupezol; Taremis; Tolbin; Tricofin; *Austral.*: Flagyl; Metrogyl; Metronide; Rozex; Zidoval; *Austria*: Anaerobex; Ariline; Elyzol†; Nidazea; Rozex; Trichex; *Belg.*: Flagyl; Nidazea; Rosaced; Rozex; *Braz.*: Canderm; Candifen; Dalzolston; Flagimax; Flagyl; Flanizol; Helmizol; Metronide†; Metroniflex†; Metronil; Metronin†; Metronix; Metroval; Metrozol†; Neo Metrodazol; Odonid†; Rozex; Trinodazol; *Canad.*: Flagyl; Florazole; MetroCream; MetroGel; MetroLotion; NidaGel; Noritate; Novo-Nidazol; Trikacide†; *Chile*: Deprocid†; Flagyl; Geloderm; Kabizol; Medazol; Metrocream; Metrogel; Metropast; *China*: Ai Di (艾迪); Ao Ke An (奥可安); Fu Shu Da (孚舒达); Hua Shi (华适); Hui He (惠和); Jia Le Ning (佳乐宁); Le Yi Fu (乐易扶); LiFu (丽芙); Mi Er Tuo (迷尔脱); Ni Mei Xin (尼美欣); Noritate (耐瑞); Shu Rui Te (舒瑞特); Tian Li Ning (天力宁); Wei Di Le (威迪乐); Ya Kang (牙康); Yi Fu Qing (一孚晴); *Cz.*: Efloran; Entizol; Rosalox; Rozex; *Denm.*: Elyzol†; Flagyl; Rozex; Zidoval; *Fin.*: Elyzol†; Flagyl; Rosazol; Rozex; Trikozol; Zidoval; *Fr.*: Collazole†; Flagyl; Grinazole; Imizine; Metrocol; Metrogene; Rosiced; Rozacreme; Rozagel; Rozex; *Ger.*: Arilin; Clont; Elyzol†; Flagyl; Infectoclont†; Metrocreme; Metrogel; Metrolotion; Metronour†; Metrosa; Rosiced; Vagi-Metro; Vagimid; *Gr.*: Acsacea; Colpocin-T; Dermaskin; Elyzol; Emedal; Flagolin; Flagyl; Gnostol; Metrazol; Metrogyl; Pedryl; Periotret; Robaz; Rosiced; Trichovagil; Tricodazole; Unitrim; *Hong Kong*: Elyzol†; Fitgyl†; Flagyl; Frotin; Gynoplix; Marpha-zole†; Metole†; Metrot; Metrogyl; Metrozole†; Nizole†; Noritate†; Qualigyl; Rozex; Syneodalin†; Unigo; *Hung.*: Klion Metrosa; Rozex; Supplin; *India*: Aldezole; Anaerid-S; Antambin; Aristogyl; Avimet; Balgyl; Compeba; Flagyl; Glucogyl; Intagyl; Ivmetro; Lupigyl; Met; Metgyl; Metris; Metrogyl; Metron Monizole; *Indon.*: Anmerob†; Biatron; Corsagyl; Dumozol; Farnat; Fladex; Flagsol; Flagyl; Flametia†; Fortagyl; Metrofusin Molazol; Nidazole; Promuba; Supplin; Tismazol; Trichodazol Trogiar; Trogyl; Vadazol; Vagizol; *Irl.*: Flagyl; Metrogel; Metronide; Metrotop†; Rozex; *Israel*: Elyzol†; Flagyl; Metrogyl; Noritate; Rozex; Venogyl†; Zidoval; *Ital.*: Deflamon; Elyzol; Flagyl Rosiced; Rozex; Vagilen; Zidoval; *Malaysia*: Flagyl†; Fogyl; Frotin; Metronol; Protogyl†; Rozex; *Mex.*: Ameblin; Biomona; Biotazol; Dasmetrol; Dualizol; Elyzol; Epaq; Fagizol; Fartricon; Flagenase; Flagenol; Flagepat; Flagyl; Flaxtec; Fresenizol Hemestal; Lagylan; Lamblit; Lozad†; Medazol†; Medizol†; Messeldazol; Metricom; Metrizol; Metrobendizol; Metrocream; Metrogel; Metroson; Milezzol; Nidralon-V; Nidrozol†; Nitromidager; Ortrizol; Otrozol; Ovazol-V†; Planizol; Promibasol; Prozolin; Samonil; Servizol†; Solumidazol†; Stomfiler; Valpar; Vanestrin-V; Vertisal; *Neth.*: Flagyl; Nidazea; Rosiced; Rozex; *Norw.*: Elyzol†; Flagyl; Rozex; Zidoval; *NZ*: Flagyl; Rozex; Trichozole; *Philipp.*: Ameryl; Anerobia†; Anerobizol; Bacimex; Clovizole; Dazomet; Flacel; Flagyl; Flamibazid; Foramebex; Globazol†; Medgyl; Metrinox; Metrodal; Metroxid; Metrozol; Microzol; Norstene; Nozol; Panazole; Patryl; Protozole; Robaz; Rodazid; Seltrozol; Servizol; Trichomar; Tricomycin; Triconex; Tridel; Vamogyl†; Zol; Zolnid; *Pol.*: Arilin; Metrosept†; Rozex; *Port.*: Dumozol; Elyzol†; Flagyl; Metroderme; Norstene; Rodermil; Roseless†; Rosiced; *Rus.*: Bacimex (Бацимекс); Ciptrogil (Сиптрогил); Efloran (Эфлоран); Flagyl (Флагил); Klion (Клион); Metrogyl (Метрогил); Metrolacare (Метролакэр); Metron (Метрон); Metroseptol (Метросептол); Metrovagin (Метровагин); Metrovit (Метровит); Metrozol (Метрозол); Rosamet (Розамет); Rozex (Розекс); Tricho-PIN (Трихо-ПИН); Trichobrol (Трихоброл); Trichopol (Трихопол); *S.Afr.*: Acuzole; Adco-Metrostat; Ambral; Amzole; Anaerobyl; Bemetrazole; Dynametron; Flagyl; Intramed Trichazole; Medamet; Metagyl; Metazol; Metrazole; Metris; Metrogel V; Narobic; Rozex; Suprazole; Trichazole; Zagyl†; Zobacide†; *Singapore*: Fladex; Flagyl; Medazole; Nizole; Protogyl; Rozex; Stanzil; Syneodalin; Trinazole; *Spain*: Amotein†; Flagyl; Rozex; Tricowas B†; Zidoval; *Swed.*: Elyzol†; Flagyl; Rosazol; Rozex; Zidoval; *Switz.*: Arilin; Dumozol; Elyzol†; Flagyl; Metrolag; Nidazea; Perilox; Rosalox; Rozex; *Thai.*: Asiazole; Biogyl†; Flagyl; Kana-P; Medazole; Medizole; Mefiron; Menisole†; Mepagyl; Metrazole; Metrizone; Metrocide; Metrogyl; Metrolex; Metrovid†; Milanidazole; Nidazole; Nidazone; Novamet; Robaz; Temonas; Tricomed; Unigo†; Vagil; Vagilan; Vagyl†; *Turk.*: Flagyl; Metrajil; Metrazol; Metrosel†; Nidazol†; Roza; *UAE*: Negazole; *UK*: Acea; Anabact; Elyzol; Flagyl; Metrogel; Metrolyl; Metrosa; Metrotop†; Metrozol; Noritate; Norzol; Rosiced; Rozex; Vaginyl; Zidoval; Zyomet; *Ukr.*: Efloran (Эфлоран); Flagyl (Флагил); Gravagin (Гравагин); Klion (Клион)†; Metrogyl (Метрогил); Trichopol (Трихопол); *USA*: Flagyl; Metrocream; Metrogel Vaginal; Metrogel; Noritate; Protostat; Rosadan; Vandazole; Vitazol†; *Venez.*: Bactrizol; Flegyl; Menizol; Metren; Metris; Metrogyl; Metrovax; Rozek.

Multi-ingredient Preparations. *Arg.*: Bexon; Ciprocort; Colpofilin Max; Estilomicin; Fangan Plus; Farm-X Duo; Farm-X Ginecologico; Flagystatin; Ginal Cent; Ginkan; Linfol Cicatrizante; Linfol; Linfol; Mailen; Metanis; Monizol Cort; Naxo TV; Neo Pelvicillin; Ovufem; Ovumix; Pelvicillin NF; Pentol; Septigyn; Tratomax; Tratomax; Vagicural Plus; Vagilen; *Austral.*: Somac-MA†; *Braz.*: Bio-Vagin; Colpatrin; Colpist; Colpistar; Colpistatin; Donnagel; Flagyl Nistatina; Fungimax; Ginestatin†; Kolpitrat; Periodontil; Tricolpex; Tricomax; Trinodazol Nistatina; Trinodazol; Vagi Biotic; Vagimax†; *Canad.*: Flagystatin; Losec 1-2-3 M; Rosasol; *China*: Bi Jie (碧洁); Shan Qing (山庆); Shuang Zuo Tai (双唑泰); Ya Zhou Kang (牙周康); *Cz.*: Klion-D; *Fin.*: Flagyl Comp; Helipak A; Helipak T; *Fr.*: Bi Missilor; Birodogyl; Missilor; Rodogyl; Tergynan; *Hung.*: Klion-D; *India*: A-Flox M; Abdogyl-N; Actinor-MZ; Aldezol-DF; Aldiagram; Aldiamycin; Alfumet; Amibex-NA; Amibex; Anaerid-F; Aristogyl Plus; Aristogyl-F; Aristogyl-F; Atodine-M; Aviflox-M; Avilox-M; Bacter-M; Bactomet; Balvidine-M; Bekker-M; Bestodin-M; Biosin; Broflox Plus; Burnoff; C-Dial; C-Flox-M; C-Met; Clingen Plus; Clofcin-M; Darmed; Dentasep; Dependal-M; Diaba-M; Diaglow; Diarlop Plus; Digyl; Dinemet-M; Diof; Drez-V; Drez; Dyrade-M; E-Dine-M; Ecoseptic; Entakon-M; Entamizole†; Enterofuran-M; Entrozyme-M; Fastaid; Fenigyl; Flagyl-F; Floxole-MZ; Flozen-M; Fogum; Fumestar; Gastogyl-M; Gramogyl; Gramogyl; Gramoneg-M; Heal; Healin; Heximet; Inseptin-MF; Iocandin Sol; Iocandin-M; Kaltin MF; Klassak; Lomostop-MF; Lotinor; Loxamet; Maghex-M; Mangogyl; Mapgyl; Matinor; Matrix-MN;

Medilop; Megaflox-M; Megyl-F; Meklin; Melam; Metnox; Metro Plus; Metro-P; Metro; Metrogyl Compound; Metrogyl-DG; Metrogyl-F; Metrogyl-P; Metrohex; Metrokind-P; Metron-DF; Metronor-P; Mexidin; Mezodin; Misodine-M; Mupimet; N-TZ; Nalidys; Negadix-M; Neocip M; Nex-M; Nitra-Met; NM Power; Nogit-M; Nor-Metrogyl; Noragyl; Norbit; Norfagyl; Norfazole; Norgrade; Norin-MZ; Normint; Norrit; Notty; Novogyl-MPS; Noxigyl; NTD; Nugit-M; Obit-M; Of-M; Ofacin-M; Oflact-M; Oflamed-MN; Oflaquin-M; Oflatoon-MZ; Oflavid; Oflee-M; Oflo-M; Oflomet; Oflostar-M; OFM; Oftec-M; Okaflox M; Okagyl; Olife-M; Orahex; Orex-M; Ovidine-M; Oxo-M; Pantop-HP; Powergyl; Qugyl; ***Indon.***: Fladystin; Flagystatin; Neo Gynoxa; Provagin; Trichostatic; Vagistin; ***Irl.***: Pylera; ***Ital.***: Meclon; ***Malaysia***: Neo-Penotran; Rodogyl; ***Mex.***: Acenil; Amebyl; Diodolina; Eskapar Compuesto; Flagenase 400; Flagocil†; Flagystatin V; Gynotran; Lambliquin; Madecassol C; Metodine; Metrodiyod; Metrofur†; Norecil; Nysmosons-V; Promibasol-Plus†; Rodogyl; Stomffler Plus; Vagitrol-V; ***Philipp.***: Flagystatin; Neo-Penotran; ***Pol.***: Gynalgin; ***Rus.***: Dentamet (Дентамет); Gynalgin (Гиналгин); Gyterna (Гитерна); Klion-D (Клион-Д); Metrogyl Denta (Метрогил Дента); Metrogyl Plus (Метрогил Плюс); Metrohex (Метрогекс); Neo-Penotran (Нео-Пенотран); ***Singapore***: Flagystatin; Neo-Penotran; ***Spain***: Blastoestimulina; Rhodogil; ***Turk.***: Gynotran; Neo-Penotran; Nidazol-M; ***Ukr.***: Dentagel (Дентагель); Gynalgin (Гиналгин); Klion-D (Клион-Д); Metrogyl Denta (Метрогил Дента); Micogynax (Микожинакс); Neo-Penotran (Нео-Пенотран); ***USA***: Helidac; Pylera.

Pharmacopoeial Preparations

BP 2014: Metronidazole Gel; Metronidazole Infusion; Metronidazole Oral Suspension; Metronidazole Suppositories; Metronidazole Tablets;

USP 36: Metronidazole Capsules; Metronidazole Gel; Metronidazole Injection; Metronidazole Tablets.

Monensin *(BAN, USAN, rINN)*

Lilly-67314; Monensina; Monensinum; Монензин.

4-[2-[2-Ethyl-3'-methyl-5'-(tetrahydro-6-hydroxy-6-hydroxymethyl-3,5-dimethylpyran-2-yl)perhydro-2,2'-bifuran-5-yl]-9-hydroxy-2,8-dimethyl-1,6-dioxaspiro[4.5]dec-7-yl]3-methoxy-2-methylpentanoic acid.

$C_{36}H_{62}O_{11}$=670.9

CAS — 17090-79-8.

ATC Vet — QA16QA06; QP51AH03.

UNII — 906O0YJ6ZP.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Monensin). A mixture of antibiotic substances produced by *Streptomyces cinnamonensis*.

Monensin Sodium *(BANM, rINNM)*

Monensin Sodique; Monensina sódica; Natrii Monensinum; Натрий Монензин.

$C_{36}H_{61}NaO_{11}$=692.9

CAS — 22373-78-0.

ATC Vet — QA16QA06; QP51AH03.

UNII — 1GS872GAFV.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Monensin Sodium). An off-white to tan crystalline powder. Slightly soluble in water; soluble in chloroform and in methyl alcohol; practically insoluble in petroleum spirit. Avoid moisture and excessive heat.

Profile

Monensin is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor for cattle.

Narasin *(BAN, USAN, rINN)*

Compound 79891; Lilly-79891; Narasina; Narasine; Narasinum; Наразин.

2-[6-[5-[2-(5-Ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-3,5-dimethylpyran-2-yl]butyric acid.

$C_{43}H_{72}O_{11}$=765.0

CAS — 55134-13-9.

ATC Vet — QP51AH04.

UNII — DZY9VU539P.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Narasin Granular). It contains narasin mixed with suitable carriers and inactive ingredients prepared in a granular form that is free-flowing and free of aggregates. Narasin is a white to off-white crystalline powder. Soluble in water and in methyl alcohol.

Profile

Narasin, an antibiotic produced by *Streptomyces aureofaciens*, is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in chickens.

Nicarbazin *(BAN)*

Nicarbazina; Никарбазин.

An equimolecular complex of 1,3-bis(4-nitrophenyl)urea ($C_{13}H_{10}N_4O_5$) and 4,6-dimethylpyrimidin-2-ol ($C_6H_8N_2O$).

$C_{19}H_{18}N_6O_6$=426.4

CAS — 330-95-0.

ATC Vet — QP51AE03.

UNII — 11P9NUA12U.

Profile

Nicarbazin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Nifuratel *(BAN, USAN, rINN)*

Methylmercadone; Nifurateeli; Nifuratelum; Нифурател.

5-Methylthiomethyl-3-(5-nitrofurfurylideneamino)-2-oxazolidone.

$C_{10}H_{11}N_3O_5S$=285.3

CAS — 4936-47-4.

ATC — G01AX05.

ATC Vet — QG01AX05.

UNII — U60U6P08SP.

Uses and Administration

Nifuratel is a nitrofuran derivative with a broad antimicrobial spectrum. It is active against the protozoan *Trichomonas vaginalis* and has an antibacterial spectrum similar to that of nitrofurantoin and some antifungal activity against *Candida albicans*. Although other drugs are preferred, nifuratel has been used to treat susceptible infections of the genito-urinary tract in oral doses of 200 to 400 mg three times daily. It has also been given vaginally.

Adverse Effects

Adverse effects associated with nifuratel include gastrointestinal disturbances, peripheral neuropathy, and thrombocytopenic purpura. Allergic reactions, hepatotoxicity, blood dyscrasias, and pulmonary reactions similar to those seen with the structurally related drug nitrofurantoin have been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given nifuratel.

Hypersensitivity. There have been a few reports of contact dermatitis associated with nifuratel,[1] including one of a man with contact dermatitis of the genitals occurring 5 hours after the first use of nifuratel ointment; the man's wife was being treated with nifuratel vaginal pessaries.[2] Vulvovaginal allergic contact dermatitis has also been reported 8 days after the first use of nifuratel vaginal suppositories.[1]

1. Helbig-D, *et al.* Vulvovaginal allergic contact dermatitis from nifuratel: report of a case and review of the literature. *Contact Dermatitis* 2008; **58**: 251–2.
2. Bedello PG, *et al.* Contact dermatitis from nifuratel. *Contact Dermatitis* 1983; **9**: 166.

Precautions

Nifuratel should not be given to patients with renal impairment, neuropathies, or G6PD deficiency.

Interactions

A disulfiram-like reaction may occur in patients taking alcohol while on nifuratel therapy.

Pharmacokinetics

When taken orally nifuratel is absorbed from the gastrointestinal tract. A metabolite, with activity against bacteria but not against trichomonads, is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Macmiror; ***Ger.***: Inimur†; ***Hong Kong***: Macmiror; ***Ital.***: Inimur; Macmiror; ***Mex.***: Macmiror; ***Pol.***: Macmiror; ***Rus.***: Macmiror (Макмирор); ***Ukr.***: Macmiror (Макмирор).

Multi-ingredient Preparations. ***China***: Lang Yi (朗依); Shui Qing (水青); ***Cz.***: Macmiror Complex; ***Hong Kong***: Macmiror Complex; ***Ital.***: Inimur Complex; Macmiror Complex; ***Mex.***: Macmiror Complex V; ***Pol.***: Macmiror Complex; ***Port.***: Dafnegil; ***Rus.***: Macmiror Complex (Макмирор Комплекс); ***Turk.***: Macmiror Complex; ***Ukr.***: Macmiror Complex (Макмирор Комплекс).

Nifursol *(BAN, USAN, pINN)*

Nifursolum; Нифурсол.

3,5-Dinitro-2'-(5-nitrofurfurylidene)salicylohydrazide.

$C_{12}H_7N_5O_9$=365.2

CAS — 16915-70-1.

ATC Vet — QP51AX05.

UNII — TG99GOU55Z.

Profile

Nifursol is an antiprotozoal that has been used in veterinary practice for the prevention of blackhead (histomoniasis) in poultry. Nifursol has been banned from use in food-producing animals in some countries because it is potentially mutagenic, carcinogenic, and genotoxic.

Nifurtimox *(BAN, rINN)*

Bayer-2502; Nifurtimoxum; Нифуртимокс.

Tetrahydro-3-methyl-4-(5-nitrofurfurylideneamino)-1,4-thiazine 1,1-dioxide.

$C_{10}H_{13}N_3O_5S$=287.3

CAS — 23256-30-6.

ATC — P01CC01.

ATC Vet — QP51AC01.

UNII — M84I3K7C2O.

Pharmacopoeias. In *Fr.* and *Int.*

Uses and Administration

Nifurtimox is a nitrofuran derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease) due to infection by *Trypanosoma cruzi*, especially the early acute stage of the disease (see p. 925.3). In African trypanosomiasis it has some activity against *T. brucei gambiense*, the organism responsible for West African sleeping sickness.

Nifurtimox is given orally in 3 to 4 divided doses. It is better tolerated by children than by adults. Treatment for **American trypanosomiasis** is given for 90 days for acute infections and 120 days for chronic infections. Doses for adults are 8 to 10 mg/kg daily. For doses in **African trypanosomiasis** see below.

For details of doses in children, see below.

Administration in children. For the treatment of American trypanosomiasis (Chagas' disease) in children, nifurtimox may be given orally in 3 or 4 divided doses for 90 to 120 days. Doses are based on age and weight:

- children from 1 to 10 years of age: 15 to 20 mg/kg
- children from 11 to 16 years of age: 12.5 to 15 mg/kg

Leishmaniasis. Mucocutaneous leishmaniasis of the New World (p. 922.1) is usually treated with pentavalent antimony or, in those who do not respond, with amphotericin B or pentamidine. However, nifurtimox 10 mg/kg daily for a minimum of 4 weeks has been shown to be effective in cases of mucocutaneous leishmaniasis in Colombia and Brazil. Despite this, toxic effects with nifurtimox are common and its role as a second-line drug or with pentavalent antimony has not been established.[1]

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793*, 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 27/07/09)

Neuroblastoma. Nifurtimox is under investigation[1] in the management of neuroblastoma (p. 716.2).

1. Saulnier Sholler GL, *et al.* A phase 1 study of nifurtimox in patients with relapsed/refractory neuroblastoma. *J Pediatr Hematol Oncol* 2011; **33**: 25–30.

African trypanosomiasis. Nifurtimox has been tried as an alternative to melarsoprol or eflornithine in the meningoencephalitic stage of *Trypanosoma brucei gambiense* infection (p. 925.2), but higher doses than those used in American trypanosomiasis are necessary. A good initial response was achieved[1] in 25 patients with nifurtimox 15 mg/kg daily for 60 days, but 3 patients relapsed while still receiving nifurtimox and a further 12 of 19 patients who were followed up relapsed subsequently. An attempt[2] to improve the response by increasing the daily dose even higher to 30 mg/kg for 30 days resulted in substantial toxicity and only a modest improvement in results, with 9 of 25 patients relapsing. Promising results have been reported[3,4] from use of oral nifurtimox 15 mg/kg daily (5 mg/kg every 8 hours) for 10 days with eflornithine 400 mg/kg daily (200 mg/kg every 12 hours) intravenously for 7 days; this drug combination (NECT) has now been included in the WHO List of Essential Medicines for the

treatment of human African trypanosomiasis,[5] and may be a candidate to replace melarsoprol in this condition.[6]

1. Pepin J, *et al.* An open clinical trial of nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness in central Zaire. *Trans R Soc Trop Med Hyg* 1989; 83: 514–17.
2. Pépin J, *et al.* High-dose nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness: an open trial in central Zaire. *Trans R Soc Trop Med Hyg* 1992; 86: 254–6.
3. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; 45: 1435–42.
4. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009; 374: 56–64.
5. WHO. WHO Model List of Essential Medicines; 16th list (updated March 2010). Available at: http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf (accessed 08/07/10)
6. Lutje V, *et al.* Chemotherapy for second-stage human African trypanosomiasis. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 02/02/11).

Adverse Effects and Precautions

Adverse effects are common with nifurtimox and include gastrointestinal effects such as anorexia, loss of weight, abdominal pain, nausea and vomiting, and effects on the nervous system, such as memory loss, insomnia, CNS excitement, convulsions, and psychotic behaviour. Long-term treatment has been associated with peripheral nervous system effects such as tremor, muscle weakness, mild paraesthesia, and polyneuropathy. Haematological adverse effects, skin rashes, and other allergic reactions may occur. Patients are advised not to drink alcoholic beverages while taking nifurtimox.

Breast feeding. Women being treated with nifurtimox for American trypanosomiasis are discouraged from breast feeding. However, based on theoretical models to estimate breast milk concentrations and milk-plasma ratio, the risk for significant infant exposure to nifurtimox through breast milk was calculated to be small and below the level of exposure of infants receiving nifurtimox treatment for American trypanosomiasis.[1] In view of these findings it was recommended that the risk of stopping breast feeding should be carefully evaluated against its benefits, particularly in poor communities with limited services.

1. Garcia-Bournissen F, *et al.* Is use of nifurtimox for the treatment of Chagas disease compatible with breast feeding? A population pharmacokinetics analysis. *Arch Dis Child* 2010; 95: 224–8.

Mutagenicity. An increase in chromosomal aberrations has been seen in children given nifurtimox.[1]

1. Gorla NB, *et al.* Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res* 1989; 224: 263–7.

Pharmacokinetics

Oral nifurtimox is well absorbed and peak serum concentrations occur after 4 hours. It is rapidly and extensively metabolised and relatively low concentrations of nifurtimox appear in the plasma and tissues. It is presumed to cross the blood-brain barrier. Less than 1% of an oral dose is excreted unchanged in the urine. The half-life is about 3 hours and is not significantly altered in those with severe renal impairment.

References.

1. Paulas C, *et al.* Pharmacokinetics of a nitrofuran compound, nifurtimox, in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* 1989; 27: 454–7.
2. Gonzalez-Martin G, *et al.* The pharmacokinetics of nifurtimox in chronic renal failure. *Eur J Clin Pharmacol* 1992; 42: 671–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Lampit.

Nimorazole *(BAN, rINN)*

Nimorazol; Nimorazolo; Nimorazolum; Nitrimidazina; Nitrimidazine; Ниморазол.

4-[2-(5-Nitroimidazol-1-yl)ethyl]morpholine.

$C_9H_{14}N_4O_3$=226.2.

CAS — 6506-37-2.

ATC — P01AB06.

ATC Vet — QP51AA06.

UNII — 469ULX0H4G.

Pharmacopoeias. In *It.*

Uses and Administration

Nimorazole is a 5-nitroimidazole derivative. It has antimicrobial actions and uses similar to those of metronidazole (p. 936.2). It is also used as a radiosensitiser.

In the treatment of **trichomoniasis**, the usual dose of nimorazole is 2 g orally as a single dose with a main meal. It may alternatively be given in a dose of 1 g every 12 hours for three doses, or 250 mg three times daily for 5 to 7 days. In **amoebiasis**, nimorazole 1 g is given twice daily, usually for 5 to 10 days and in **giardiasis** a dose of 500 mg is given twice daily, usually for 5 to 7 days.

Nimorazole may also be used in the treatment of **acute ulcerative gingivitis** in a dose of 500 mg twice daily for 2 days.

Radiosensitisation. References to the use of nimorazole as a radiosensitiser in the management of head and neck cancer.

1. Overgaard J, *et al.* A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma: results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. *Radiother Oncol* 1998; 46: 135–46.
2. Henk JM, *et al.* Treatment of head and neck cancer with CHART and nimorazole: phase II study. *Radiother Oncol* 2003; 66: 65–70.
3. Overgaard J, *et al.* Plasma osteopontin, hypoxia, and response to the hypoxia sensitiser nimorazole in radiotherapy of head and neck cancer: results from the DAHANCA 5 randomised double-blind placebo-controlled trial. *Lancet Oncol* 2005; 6: 757–64.
4. Bjarnason NH, *et al.* The nimorazole regimen in patients with head and neck cancer can increase the effect of vitamin K antagonists. *Acta Oncol* 2008; 47: 150–1.

Adverse Effects and Precautions

As for Metronidazole, p. 937.3.

Pharmacokinetics

Nimorazole is readily absorbed from the gastrointestinal tract. Peak blood concentrations occur within 2 hours, and high concentrations are reported to occur in salivary and vaginal secretions. Trichomonicidal urinary concentrations may persist for up to 48 hours after a dose. It is mainly excreted in the urine as metabolites that also have some antiprotozoal and antibacterial activity. Unchanged drug and metabolites also appear in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Naxogin; *Belg.*: Naxogin†; *Braz.*: Naxogin; *Gr.*: Naxogin; *Rus.*: Naxogin (Наксоджин); *Turk.*: Naksojin; *Ukr.*: Naxogin (Наксоджин).

Multi-ingredient Preparations. *Braz.*: Naxogin Composto; *Chile*: Naxogin Compositum†; *Indon.*: Gynoxa; Naxogin Complex.

Nitazoxanide *(BAN, USAN, rINN)*

Nitazoxanida; Nitazoxanidum; PH-5776; Нитазоксанид.

N-(5-Nitro-2-thiazolyl)salicylamide acetate.

$C_{12}H_9N_3O_5S$=307.3.

CAS — 55981-09-4.

ATC — P01AX11.

UNII — SOA12P041N.

Uses and Administration

Nitazoxanide is used for the treatment of cryptosporidiosis (p. 921.1) and giardiasis (p. 921.3). It is given orally and should be taken with food; the usual dose is 500 mg twice daily for 3 days.

For details of doses in children, see below.

Nitazoxanide has also been tried in several other protozoal and helminth infections, particularly in immunocompromised patients, including those with HIV infection. It is also being investigated for the treatment of chronic hepatitis C, rotavirus disease, and *Clostridium difficile* colitis. For further information see below.

Reviews.

1. Bailey JM, Erramouspe J. Nitazoxanide treatment for giardiasis and cryptosporidiosis in children. *Ann Pharmacother* 2004; 38: 634–40.
2. Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis* 2005; 40: 1173–80.
3. Musher DM, *et al.* Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006; 43: 421–7.
4. Anderson VR, Curran MP. Nitazoxanide: a review of its use in the treatment of gastrointestinal infections. *Drugs* 2007; 67: 1947–67.

Administration in children. For the treatment of cryptosporidiosis and giardiasis in children, nitazoxanide is given orally with food. Doses are 100 mg twice daily for 3 days in those aged 1 to 3 years and 200 mg twice daily for 3 days in those aged 4 to 11 years.

Antibiotic-associated colitis. *Clostridium difficile* colitis is usually treated with metronidazole but treatment failures are increasingly being reported and there is concern over the emergence of vancomycin resistance if it is used for treatment instead. Nitazoxanide is therefore being investigated as a possible alternative to metronidazole. A prospective, randomised, double-blind study[1] found that nitazoxanide (at an oral dose of 500 mg twice daily for 7 to 10 days) was at least as effective as metronidazole given at a dose of 250 mg 4 times daily for 10 days. A further study[2] in 35 patients who failed treatment with metronidazole for *C. difficile* colitis and were then treated with nitazoxanide reported initial cure rates of 74% after 10 days. However, 7 patients later had recurrent disease. Three of the patients who failed initial treatment and one of those who had recurrent disease were re-treated and responded to nitazoxanide, giving an aggregate cure with nitazoxanide of 66%.

1. Musher DM, *et al.* Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006; 43: 421–7.
2. Musher DM, *et al.* Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide. *J Antimicrob Chemother* 2007; 59: 705–10.

Hepatitis C. Nitazoxanide, given orally, either as monotherapy or with peginterferon alfa-2a (with or without ribavirin) is being investigated for the treatment of chronic hepatitis C (p. 952.1).

Nitazoxanide monotherapy (500 mg twice daily for 24 weeks) in patients with chronic hepatitis C genotype 4 resulted in sustained virologic response (undetectable serum hepatitis C virus RNA 24 weeks after the end of therapy) in 17% (4 of 23) of patients; all responders had baseline serum hepatitis C virus RNA levels ≤400 000 IU/mL.[1] A later phase II study,[2] in treatment-naive patients with chronic hepatitis C genotype 4, given 12 weeks of lead-in treatment with nitazoxanide monotherapy followed by a further 36 weeks of treatment with additional peginterferon alfa-2a (with or without ribavirin) reported an increase in the percentage of patients with sustained virologic response compared with standard therapy of peginterferon alfa-2a plus ribavirin for 48 weeks. A similar study[3] in patients with mainly hepatitis C genotype 4 infection found that the lead-in treatment time for nitazoxanide monotherapy could be reduced from 12 weeks to 4 weeks without compromising sustained virologic response rates.

1. Rossignol JF, *et al.* Clinical trial: randomized, double-blind, placebo-controlled study of nitazoxanide monotherapy for the treatment of patients with chronic hepatitis C genotype 4. *Aliment Pharmacol Ther* 2008; 28: 574–80.
2. Rossignol JF, *et al.* Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon, and ribavirin. *Gastroenterology* 2009; 136: 856–62.
3. Rossignol JF, *et al.* Treatment of chronic hepatitis C using a 4-week lead-in with nitazoxanide before peginterferon plus nitazoxanide. *J Clin Gastroenterol* 2010; 44: 504–9.

Protozoal infections. As well as its established use in cryptosporidiosis (p. 921.1) and giardiasis (p. 921.3), nitazoxanide has been used in other protozoal infections including intestinal amoebiasis (p. 919.1), blastocystosis (p. 920.3), cutaneous leishmaniasis (p. 922.1), and microsporidiosis (p. 924.1).

Rotavirus diarrhoea. A randomised double-blind placebo-controlled study[1] in 38 children (median age 11 months) with confirmed rotavirus diarrhoea found that oral nitazoxanide 7.5 mg/kg twice daily for 3 days significantly reduced the duration of rotavirus disease. The median time to resolution of illness after the first dose was 31 hours for those given nitazoxanide compared with 75 hours for those given placebo. Another, single-blind study[2] involving 147 children found nitazoxanide tended to be more effective than probiotics in reducing duration of diarrhoea and time in hospital.

1. Rossignol J-F, *et al.* Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. *Lancet* 2006; 368: 124–9.
2. Teran CG, *et al.* Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *Int J Infect Dis* 2009; 13: 518–23.

Worm infections. Nitazoxanide has been used in various helminthiases, including ascariasis (p. 143.3), hymenolepiasis (p. 146.1), the liver fluke infection fascioliasis (p. 146.2), and trichuriasis (p. 149.1).

Adverse Effects

The most common adverse effects associated with nitazoxanide are abdominal pain, diarrhoea, nausea, vomiting, and headache. Other less commonly reported adverse effects include anorexia, fever, flatulence, pruritus, and dizziness. Spontaneous bone fracture and discoloration of urine and of the eyes have been reported rarely. Increased creatinine and liver enzyme values have been noted.

Pharmacokinetics

Nitazoxanide is absorbed from the gastrointestinal tract after oral dosage and is rapidly hydrolysed to an active desacetyl metabolite, tizoxanide. Tizoxanide then partially undergoes conjugation, mainly by glucuronidation. The extent of absorption is enhanced if given with food and peak plasma concentrations of tizoxanide and the glucuronide are seen 1 to 4 hours after an oral dose. The parent drug is not detected in plasma. Tizoxanide is more than 99% bound to plasma proteins. About two-thirds of an oral dose of nitazoxanide is eliminated in the faeces and one-third in the urine; tizoxanide is excreted in the urine, bile, and faeces, while the glucuronide is excreted in only the urine and bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nixoran; *Braz.*: Annita; *India*: Netazox; Nitacure; Nitarid; Nitazet; Nitzix; Nizonide; *Nozoa*: *Mex.*: Avisan; Bionit; Daxon; Dexidex; Kidonax; Mitafar; Padovan Ton; Paramix; Parsenida; Rosanil; Zotanixin; *USA*: Alinia; *Venez.*: Celectan.

Multi-ingredient Preparations. *India*: Abof-NZ; Bacter-NZ; Bestoflox N; Flagynor; Floxine-NT; Floxole-NT; Inflobid-NXT; Netazox-OF; Nita-O; Nitazet-O; Nitzix-O; Nizonide-O; Ofcare-NT; Oflee-NT; Olpit-NZ; Osani-NT; Oxalic-NZ; *Mex.*: Heliton.

Ornidazole *(USAN, rINN)*

Ornidatsoli; Ornidazol; Ornidazolum; Ro-7-0207; Орнидазол.

1-Chloro-3-(2-methyl-5-nitroimidazol-1-yl)propan-2-ol.

$C_7H_{10}ClN_3O_3$=219.6

CAS — 16773-42-5.

ATC — G01AF06; J01XD03; P01AB03.

ATC Vet — QG01AF06; QJ01XD03; QP51AA03.

UNII — 62XCK0G93T.

Uses and Administration

Ornidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p. 936.2) in the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections (p. 173.1).

It is given orally after food, or intravenously. Intravenous solutions of ornidazole should be diluted to 5 mg or less per mL and 100 or 200 mL infused over 15 to 30 minutes.

In **amoebiasis** (p. 919.1), 500 mg of ornidazole is given orally twice daily for 5 to 10 days. Patients with amoebic dysentery may be given 1.5 g as a single daily dose for 3 days. An alternative regimen for adults over 60 kg is 1 g twice daily for 3 days. In severe amoebic dysentery and amoebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 0.5 to 1 g initially, followed by 500 mg every 12 hours for 3 to 6 days.

In **giardiasis** (p. 921.3), 1 or 1.5 g of ornidazole is given orally as a single daily dose for 1 or 2 days.

In **trichomoniasis** (p. 925.1), a single oral dose of 1.5 g is given; alternatively, a 5-day oral course of ornidazole 500 mg twice daily may be used. Sexual partners should also be treated.

For the *treatment* of **anaerobic bacterial infections**, ornidazole is given by intravenous infusion in an initial dose of 0.5 to 1 g, followed by 1 g daily as a single dose or in two divided doses for 5 to 10 days; oral therapy with 500 mg every 12 hours should be substituted as soon as possible.

For the *prevention* of postoperative anaerobic bacterial infections, 1 g is given by intravenous infusion about 30 minutes before surgery. An alternative oral regimen is 1.5 g given 12 hours before surgery, then 500 mg every 12 hours for 3 to 5 days after the surgery.

For details of doses in **children**, see below.

Administration in children. Ornidazole is licensed in several countries in children weighing up to 35 kg for the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections. It is given orally after food or intravenously. Children weighing over 35 kg may be given the adult dose (above).

In **amoebiasis** children may be given an oral dose of 25 mg/kg as a single daily dose for 5 to 10 days. Those with amoebic dysentery may be given 40 mg/kg as a single daily dose for 3 days. In severe amoebic dysentery and amoebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 20 to 30 mg/kg daily for 3 to 6 days. In **giardiasis**, 30 or 40 mg/kg is given orally as a single daily dose for 1 or 2 days and in **trichomoniasis**, a single oral dose of 25 mg/kg is given.

For the treatment of **anaerobic bacterial infections**, ornidazole is given by intravenous infusion in a dose of 10 mg/kg every 12 hours for 5 to 10 days or orally at a dose of 20 to 30 mg/kg daily. For the prevention of postoperative anaerobic bacterial infections, 20 to 30 mg/kg may be given orally or intravenously 12 hours before surgery; after surgery a dose of 20 to 30 mg/kg is given every 12 hours for 3 days.

Administration in hepatic impairment. In view of the prolonged half-life and reduced clearance of ornidazole reported in patients with hepatic dysfunction (see below), the interval between doses should be doubled in patients with severe hepatic impairment.

Administration in renal impairment. The elimination of ornidazole is reported to be largely unaltered in patients with impaired renal function (see under Pharmacokinetics, below). Dosage adjustment is therefore usually unnecessary, although patients receiving haemodialysis should be given a supplemental dose of ornidazole (oral or intravenous formulations) with each dialysis run; licensed product information for an oral formulation of ornidazole suggests a supplemental dose of 500 mg should be given if the daily dose is 2 g daily or 250 mg should be given if the daily dose is 1 g daily.

Rheumatoid arthritis. Rheumatoid arthritis is common in patients with periodontitis and many pathological aspects of the diseases are similar. Furthermore, high concentrations of antibodies to anaerobic bacteria have been found in the serum and synovial fluid of patients with rheumatoid arthritis. To evaluate the efficacy of ornidazole, a randomised, double-blind, placebo-controlled study[1] was carried out in 160 patients with active rheumatoid arthritis. Significantly more patients given oral ornidazole 1 g daily met the American College of Rheumatology criteria for 20, 50 and 70% improvement at 3 months compared with those taking placebo. Ornidazole treatment was also associated with significant reductions in pain, duration of morning stiffness, and disease activity and improved quality of life.

1. Ogrendik M. Treatment of rheumatoid arthritis with ornidazole: a randomized, double-blind, placebo-controlled study. *Rheumatol Int* 2006; 26: 1132–7.

Adverse Effects and Precautions

As for Metronidazole, p. 937.3.

Effects on the liver. Auto-immune hepatitis occurred in a 35-year-old woman after treatment with ornidazole for diarrhoea and a further episode occurred after treatment for a vaginal infection.[1] A few cases of acute cholestatic hepatitis have also been reported; all the patients improved 1 to 2 months after stopping treatment.[2] Severe hepatitis with prolonged cholestasis and bile duct injury has been reported after long-term use (8 weeks) of ornidazole.[3]

1. *Koşar Y, et al.* Ornidazole-induced autoimmune hepatitis. *Eur J Gastroenterol Hepatol* 2001; 13: 737–9.
2. Tabak F, *et al.* Ornidazole-induced liver damage: report of three cases and review of the literature. *Liver Int* 2003; 23: 351–4.
3. Harputluoglu MM, *et al.* Severe hepatitis with prolonged cholestasis and bile duct injury due the long-term use of ornidazole. *Acta Gastroenterol Belg* 2007; 70: 293–5.

Pharmacokinetics

Ornidazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within 3 hours. After repeated oral doses of 500 mg every 12 hours, steady-state peak and trough concentrations are 14 and 6 micrograms/mL respectively.

The plasma elimination half-life of ornidazole is 12 to 14 hours. Less than 15% is bound to plasma proteins. It is widely distributed in body tissues and fluids, including the CSF.

Ornidazole is metabolised in the liver and is excreted in the urine, mainly as conjugates and metabolites, and to a lesser extent in the faeces. Biliary excretion may be important in the elimination of ornidazole and its metabolites.

References.

1. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy* 1976; 22: 19–29.
2. Matheson I, *et al.* Plasma levels after a single oral dose of 1.5 g ornidazole. *Br J Vener Dis* 1977; 53: 236–9.
3. Schwartz DE, *et al.* Metabolic studies of ornidazole in the rat, in the dog and in man. *Xenobiotica* 1979; 9: 571–81.
4. Turcant A, *et al.* Pharmacokinetics of ornidazole in neonates and infants after a single intravenous infusion. *Eur J Clin Pharmacol* 1987; 32: 111–13.
5. Martin C, *et al.* Pharmacokinetics and tissue penetration of a single dose of ornidazole (1,000 milligrams intravenously) for antibiotic prophylaxis in colorectal surgery. *Antimicrob Agents Chemother* 1990; 34: 1921–4.
6. Bourget P, *et al.* Disposition of ornidazole and its metabolites during pregnancy. *J Antimicrob Chemother* 1995; 35: 691–6.

Hepatic impairment. The elimination of ornidazole after a single intravenous dose of 500 mg was impaired in 10 patients with severe liver cirrhosis when compared with 10 healthy subjects; mean half-lives were 21.9 hours and 14.1 hours respectively.[1] These results suggested that the interval between doses of ornidazole should be doubled in patients with marked hepatic impairment. The need for dose adjustment was confirmed in further studies of patients with other forms of liver disease.[2,3]

1. Taburet AM, *et al.* Pharmacokinetics of ornidazole in patients with severe liver cirrhosis. *Clin Pharmacol Ther* 1986; 40: 359–64.
2. Bourget P, *et al.* Ornidazole pharmacokinetics in several hepatic diseases. *J Pharmacol Clin* 1988; 7: 25–32.
3. Taburet AM, *et al.* Pharmacokinetics of ornidazole in patients with acute viral hepatitis, alcoholic cirrhosis, and extrahepatic cholestasis. *Clin Pharmacol Ther* 1989; 45: 373–9.

Renal impairment. The half-life of intravenous ornidazole was not prolonged in a study in patients with advanced chronic renal failure, including those on continuous ambulatory peritoneal dialysis, although total plasma clearance was halved; modification of the usual dosage is not necessary in such patients. However, the drug was removed by haemodialysis and ornidazole should be given after the dialysis session rather than before.[1] In another study[2] the systemic availability and total body clearance of ornidazole were unaffected in chronic renal failure; it was considered that an additional dose should be given before haemodialysis to compensate for removal during that procedure.

1. Merdjan H, *et al.* Pharmacokinetics of ornidazole in patients with renal insufficiency: influence of haemodialysis and peritoneal dialysis. *Br J Clin Pharmacol* 1985; 19: 211–17.
2. Horber FF, *et al.* High haemodialysis clearance of ornidazole in the presence of a negligible renal clearance. *Eur J Clin Pharmacol* 1989; 36: 389–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mebaxol; *Belg.*: Tiberal; *Chile*: Invigan†; *China*: Ao Bo Lin (奥博林); Ao Li Tuo (奥立妥); AoNing (傲宁); Gu Te (固特); Heng Bo Lai (衡博来); Jin Da (今达); Mei Er Kai (美尔凯); Nei De Zi (内德滋); Pusili (普司立); Qi Ke (齐克); Rui Shen (瑞申); Sheng Nuo (圣诺); Sheng Nuo An (圣诺安); Sheng Nuo Kang (圣诺康); Tai Fang (泰方); Tuo Su (妥苏); Xiao Ran (潇然); Ya Jie (亚洁); You Lun (优伦); *Cz.*: Avrazor†; *Fr.*: Tiberal; *Gr.*: Betiral; *India*: Asiflox-OZ; Aurnida; CGDole; Dazolic; Entamizole Plus; Giro; Horn; Nidazole; Nidoba; Oflatoon-OZ; Onidaz; Oniz; Orbest; Ord; Orizole; Orni; Ornida; Orniden; Ornimax; Ornivir; Ornizen; Zil; *NZ*: Tiberal; *Rus.*: Dazolic (Дазолик); Giro (Гайро); Lornizol (Лорнизол); Orniona (Орнионa); Ornisid (Орнисид); Tiberal (Тиберал); *Switz.*: Tiberal; *Turk.*: Bitazol; Biteral; Borneral; Ornidone; Orniject; Ornisid; Ornitop; Pronizol; *Ukr.*: Ornigil (Орнигил); Ornisid (Орнисид); Ornizol (Орнизол); Tiberal (Тиберал)†.

Multi-ingredient Preparations. *India*: A-Flox-OZ; Abof-OZ; Adeflox-O; AP-Kit; Aflox-OZ; Aleflox-OZ; Alocin-OZ; Alox-OD; Ariflox-OZ; Arilif-OZ; Armbid OZ; Arviflox-OZ; Atoflox-OZ; Avidox-OZ; Aviflox-OZ; Bacter-OZ; Bactezoa-LB; Bactoff-OZ; Baseflox OZ; Bekker-OZ; Biofast-OZ; Bonflox; Brakke; Bru-OZ; C-Flox-OZ; Candifem; Canocin-OZ; Casflox-OZ; Cefit-OZ; Chekmet-O; Cifran-OZ; Cinflox-OZ; Cipnet-OZ; Covax-OZ; Cozan-O; Cucin-O; Diragyl; Dox-M-OZ; Ducidal-OZ; Duochek; Ecoflox-OZ; Edilox-OZ; Essasin-OZ; Esterflox-OZ; Eufox-O; Evopic-OZ; Fatiflox-OZ; Fern; Festive-OZ; Fixiflox-OZ; Flex-OZ; Flexril-Ord; Flobacin-OZ; Flogard-O; Flow-OZ; Floxaquin-O; Floxar-OZ; Floxine-OZ; Floxole-OZ; Flozen-OZ; Fouz; Fungid-OR; Fynal-OZ; Garnid; Gatigram-OZ; Gatikind-OZ; Gatimore-OZ; Gatiquin Oz Kit; Gatri-OZ; Gatrid-OZ; Gatrix; Gazal-O; Geryl-O; GFlox-OZ; Gic-O; Glofty-OZ; Hoflo-O; Hoflox-O; Indocin-OZ; Indof OZ; Inflobact-OZ; Inflobid-OZ; Inflox-OZ; Infoxin-OZ; Inogat-O; Intragat-O; Jflo-OZ; Kareof-OZ; Kooz; Kureflox-OZ; Kylevo-OZ; L-Cin-OZ; Laflox-O; Lamizol-O; Lebact-O; Lefosym-OZ; Lek-OZ; Levact-OZ; Levocide-OZ; Levocos-OZ; Levoflox Oz; Levogyl; Levospan-OZ; Levosym-OZ; Lexof-OZ; Logflox-OZ; Loobid; Lumigard; Magof-OZ; Mahacef-OZ; MCFlox-OZ; Meganor; Meuflox-OZ; Mintof-OZ; Mof-OZ; Moflo-OZ; Myconor-4; NBox-OZ; Neva-OZ; Niolox-OZ; Noff-OR; Noragyl-OZ; Normet; Norrit-Ord; Novaflox-OZ; Nuforce-3 Kit; O & O; O-Cebran-O; O-Cebran-OZ; O-Fact-OZ; O2; O2H; Obactin-OZ; Obid-OZ; Obit-OZ; Ocimix; Ociz-OR; Odicip-OZ; Ofac-O; Ofacin-O; Ofal-M; Ofal-OZ; Ofbid-OZ; Ofcare-OD; Ofcura-OZ; Ofdaz; Ofet-O; Ofia-OZ; Ofkab-OZ; Ofkair-OZ; Ofla-OZ; Oflab-OZ; Oflact-OZ; Oflagard-O; Oflagard-OL; Oflage-OZ; Oflamed-OZ; Oflaquin-OZ; Oflark-O; Oflas-OZ; Oflaset-OZ; Oflawin-OZ; Oflee-OZ; Oflem-OZ; Oflict-OZ; Oflina-OZ; Oflo-OZ; Oflocos-OZ; Ofloday-OZ; Ofloden-O; Ofloine-OZ; Oflomil-OZ; Oflon-OZ; Oflopar-OR; Oflopip-O; Ofloren-OZ; Oflostar-OZ; Oflotas-OZ; Oflotec-OZ; Ofly-OZ; Ofmed-OZ; Ofnet-OZ; Ofnida-LB; Ofnida; Ofnis-OZ; Ofo-OZ; Ofor-OZ; Ofpil-O; Ofral-OZ; Ofran-OZ; Ofsis-OZ; Ofspan-OZ; Ofspin-OZ; Oftacin-OZ; Oftech-OZ; Oftum-OZ; Oftwo; Ofwin-OZ; Ofzac-OZ; Ofzen-OZ; Ofzo; Ojen-OZ; Okil-OZ; Oks-OZ; Oley-OZ; Olfi-O; Olfic-OZ; Olfon-OR; Olife-OZ; Olpit-OZ; On-OZ; Oniz-O; Opeq-OZ; Ophar-OZ; OQN-O; Oqueen-OZ; Orflaz Kit; Orflo; Orflo; Orin-O; Orni-O; Ornicef; Ornidox; Orniflox; Ornilox; Ornof; Oro-flox-OZ; Osani-O; Osflox-OR; Osiflox-OZ; Ospol-OZ; Ot; Otago-O; Otic-O; Oxacin-OZ; Oxcin-Ord; Oxdrin-Ord; Oxiflox-OZ; Oxit-OZ; Oxo-Ord; Oxoism-OZ; Oxwal-OZ; Oxyna; Oza-O; Tar-iflox Plus; *Ukr.*: Neotrizol (Неотризол); Ofor (Офор); Onristat (Орнистат)†; Orcipol (Орципол); Tiflox (Тифлокс)†.

Paromomycin Sulfate *(BANM, rINNM)*

Aminosidin Sulphate; Aminosidine Sulphate; Catenulin Sulphate; Crestomycin Sulphate; Estomycin Sulphate; Hydroxymycin Sulphate; Monomycin A Sulphate; Neomycin E Sulphate; Paromomicina, sulfato de; Paromomycin Sulphate; Paromomycine, Sulfate de; Paromomycini Sulfas; Paucimycin Sulphate; Sulfato de aminosidina; Sulfato de catelubina; Sulfato de estomicina; Sulfato de hidroximicina; Sulfato de paromomicina; Sulfato de povicimina; Паромомицина Сульфат.

O-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-*O*-β-D-ribofuranosyl-(1→5)-*O*-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine sulphate.

$C_{23}H_{45}N_5O_{14}xH_2SO_4$

CAS — 59-04-1 (paromomycin); 7542-37-2 (paromomycin); 1263-89-4 (paromomycin sulfate).
ATC — A07AA06.
ATC Vet — QA07AA06.
UNII — 845NU6GJPS.

Pharmacopoeias. In *Chin.*, *Int.*, *It.*, and *US.*

USP 36: (Paromomycin Sulfate). The sulfate salt of an antibiotic substance produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, or a mixture of two or more such salts.

A creamy-white to light yellow, odourless or practically odourless, very hygroscopic powder. It loses not more than 5% of its weight on drying. Very soluble in water; insoluble in alcohol, in chloroform, and in ether. pH of a 3% solution in water is between 5.0 and 7.5. Store in airtight containers.

Uses and Administration

Paromomycin is an aminoglycoside antibacterial that has been given orally in the treatment of intestinal protozoal infections, including amoebiasis, cryptosporidiosis, and giardiasis. It has also been tried parenterally for visceral, and topically for cutaneous, leishmaniasis (below). For details of these infections and their treatment, see under Choice of Antiprotozoal, p. 919.1. It has been used in the treatment of beef or pork tapeworm infection (p. 148.2), but it is not the treatment of choice. Like neomycin (p. 330.1), it has been used in the suppression of intestinal flora pre-operatively and as adjunctive therapy in the management of hepatic encephalopathy.

Paromomycin is given as the sulfate although doses are expressed in terms of the base. In intestinal **amoebiasis**, the dose for both adults and children is the equivalent of paromomycin 25 to 35 mg/kg daily in 3 divided oral doses with meals for 5 to 10 days. Similar doses have been tried in **cryptosporidiosis**.

In taeniasis and other **tapeworm infections**, a dose of 4 g is given orally as a single dose or in divided doses over the course of one hour.

For **hepatic coma**, 4 g is given daily in divided oral doses at regular intervals for 5 to 6 days.

Administration in children. Paromomycin may be given to children for the treatment of intestinal **amoebiasis**. Oral doses used are the same as those for adults, above. For the treatment of **visceral leishmaniasis** in the Indian subcontinent, WHO recommends an intramuscular dose of paromomycin of 11 mg/kg daily for 21 days for children weighing more than 5 kg; for visceral leishmaniasis in east Africa the same intramuscular dose is recommended (with pentavalent antimonials) for 17 days.[1]

1. WHO. *WHO model formulary for children.* Geneva: WHO, 2010. Also available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 13/12/10)

Leishmaniasis. Topical treatment with paromomycin 15% plus methylbenzethonium chloride 5 or 12% has produced variable results[1-4] in **cutaneous leishmaniasis** (p. 922.1); paromomycin 12 to 15% with urea 10% was better tolerated,[5,6] however, benefit has not been seen in all studies.[4,6] Treatment with topical paromomycin plus systemic meglumine antimonate was initially promising in patients with New World cutaneous leishmaniasis;[7] however, a subsequent study[8] found no clear advantage over treatment with meglumine antimonate alone. Good responses to parenteral paromomycin 14 mg/kg daily, with sodium stibogluconate 10 mg/kg daily, in cases of *diffuse* cutaneous leishmaniasis have also been reported.[9]

Paromomycin has also been used intramuscularly, either alone[10] or with sodium stibogluconate,[11] in the treatment of **visceral leishmaniasis** (p. 923.1) in an area of India with increasing resistance to pentavalent antimony compounds. The authors of one study[10] found paromomycin 16 or 20 mg/kg daily for 21 days to be significantly more effective than sodium stibogluconate 20 mg/kg daily for 30 days, while another study[12] found intramuscular paromomycin (11 mg/kg) daily for 21 days to be no less effective than treatment with intravenous amphotericin B (1 mg/kg) on alternate days for 30 days. Although patients given intramuscular paromomycin (11 mg/kg) daily for 14 days showed significant improvement in clinical and biomedical parameters, they had a statistically significant lower cure rate than those given treatment for 21 days; this 14-day treatment regimen is therefore not recommended as monotherapy.[13] WHO recommends an intramuscular dose of 11 mg/kg daily for 21 days for all patients weighing more than 5 kg.[14] Oral paromomycin plus intravenous pentamidine was reported to be effective in the treatment of amphotericin-resistant visceral leishmaniasis in an HIV-infected patient.[15]

1. El-On J, *et al.* Topical treatment of Old World cutaneous leishmaniasis caused by Leishmania major: a double-blind control study. *J Am Acad Dermatol* 1992; **27**: 227–31.
2. Krause G, Kroeger A. Topical treatment of American cutaneous leishmaniasis with paromomycin and methylbenzethonium chloride: a clinical study under field conditions in Ecuador. *Trans R Soc Trop Med Hyg* 1994; **88**: 92–4.
3. Arana BA, *et al.* Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. *Am J Trop Med Hyg* 2001; **65**: 466–70.
4. Asilian A, *et al.* A randomized, placebo-controlled trial of a two week regimen of aminosidine (paromomycin) ointment for treatment of cutaneous leishmaniasis in Iran. *Am J Trop Med Hyg* 1995; **53**: 648–51.
5. Bryceson ADM, *et al.* Treatment of Old World cutaneous leishmaniasis with aminosidine ointment: results of an open study in London. *Trans R Soc Trop Med Hyg* 1994; **88**: 226–8.
6. Ben Salah A, *et al.* A randomized, placebo-controlled trial in Tunisia treating cutaneous leishmaniasis with paromomycin ointment. *Am J Trop Med Hyg* 1995; **53**: 162–6.
7. Soto J, *et al.* Successful treatment of New World cutaneous leishmaniasis with a combination of topical paromomycin/methylbenzethonium chloride and injectable meglumine antimonate. *Clin Infect Dis* 1995; **20**: 47–51.
8. Soto J, *et al.* Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimonate as treatment for American cutaneous leishmaniasis: controlled study. *Clin Infect Dis* 1998; **26**: 56–8.
9. Teklemariam S, *et al.* Aminosidine and its combination with sodium stibogluconate in the treatment of diffuse cutaneous leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1994; **88**: 334–9.
10. Jha TK, *et al.* Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. *BMJ* 1998; **316**: 1200–5.
11. Thakur CP, *et al.* A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. *Trans R Soc Trop Med Hyg* 2000; **94**: 429–31.
12. Sundar S, *et al.* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; **356**: 2571–81.
13. Sundar S, *et al.* Short-course paromomycin treatment of visceral leishmaniasis in India: 14-day vs 21-day treatment. *Clin Infect Dis* 2009; **49**: 914–18.
14. WHO. *WHO model formulary.* Geneva: WHO, 2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/12/10)
15. Manfredi R, *et al.* Diffuse cutaneous dissemination of visceral leishmaniasis during human immunodeficiency virus (HIV) infection, despite negligible immunodeficiency: repeated failure of liposomal amphotericin B administration, followed by successful long-term pentamidine and paromomycin administration. *Int J Antimicrob Agents* 2008; **31**: 590–2.

Trichomoniasis. Local application of a paromomycin cream has been tried in a small number of patients with metronidazole-resistant vaginal trichomoniasis (p. 925.1) with moderate success.[1] Intravaginal use of 250-mg oral tablets of paromomycin twice daily in a similar patient has also been reported.[2] The patient became asymptomatic within 3 weeks of starting paromomycin despite stopping treatment after 10 days because of vaginal soreness.

1. Nyirjesy P, *et al.* Difficult-to-treat trichomoniasis: results with paromomycin cream. *Clin Infect Dis* 1998; **26**: 986–8.
2. Tayal SC, *et al.* Paromomycin treatment of recalcitrant *Trichomonas vaginalis*. *Int J STD AIDS* 2010; **21**: 217–18.

Adverse Effects, Treatment, and Precautions

As for Neomycin, p. 330.2.

Effects on electrolytes. Three cases of tetany have been described in patients being treated for leishmaniasis with parenteral paromomycin. Symptoms resolved after treatment with intravenous calcium gluconate and paromomycin treatment could be continued with oral calcium supplementation.[1] The authors consider that paromomycin may cause temporary renal tubular damage leading to hypocalcaemia.

1. Thakur CP. Tetany in kala azar patients treated with paromomycin. *Indian J Med Res* 2008; **127**: 489–93.

Effects on the pancreas. Pancreatitis was associated with use of paromomycin during treatment of cryptosporidiosis in a patient with HIV infection.[1]

1. Tan WW, *et al.* Paromomycin-associated pancreatitis in HIV-related cryptosporidiosis. *Ann Pharmacother* 1995; **29**: 22–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paromomycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for Neomycin, p. 330.3.

Antimicrobial Action

Paromomycin is active against various protozoa including *Leishmania* spp., *Entamoeba histolytica*, and *Cryptosporidium* spp. In addition, it has an antibacterial spectrum similar to that of neomycin (p. 330.3). There is cross-resistance between paromomycin and kanamycin, framycetin, neomycin, and streptomycin.

Paromomycin also has anthelmintic properties against tapeworms.

Pharmacokinetics

Paromomycin is poorly absorbed from the gastrointestinal tract and most of an oral dose is eliminated unchanged in the faeces; about 0.1% of an oral daily dose is excreted renally. Oral absorption may be increased in conditions which damage or inflame the mucosa or disrupt gastrointestinal motility.

Peak plasma concentrations are reached within 0.5 to 1.5 hours after an intramuscular injection. After intramuscular use it distributes well into extracellular fluid, but penetrates poorly into the CNS and lungs. Paromomycin crosses the placenta and may accumulate in amniotic fluid and fetal plasma. The plasma elimination half-life is 2.62 hours. Paromomycin does not appear to be metabolised and is excreted virtually unchanged in the urine by glomerular filtration.

Parenteral administration. References.

1. Kanyok TP, *et al.* Pharmacokinetics of intramuscularly administered aminosidine in healthy subjects. *Antimicrob Agents Chemother* 1997; **41**: 982–6.
2. Sundar S, *et al.* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; **356**: 2571–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Humatin; *Belg.*: Gabbroral; *Canad.*: Humatin; *Ger.*: Humatin; *Gr.*: Humatin; *Indon.*: Gabbryl; *Ital.*: Gabbroral; Humatin; Kaman; *Jpn*: Ameparomo; *Spain*: Humatin; *Switz.*: Humatin; *USA*: Humatin.

Multi-ingredient Preparations. *Israel*: Leshcutan.

Pharmacopoeial Preparations

USP 36: Paromomycin Sulfate Capsules; Paromomycin Sulfate Syrup.

Pentamidine Isetionate *(BANM, rINNM)*

Isetionato de pentamidina; M&B-800; Pentamidiinidiisetionaatti; Pentamidin Izetiyonat; Pentamidina, isetionato de; Pentamidindiisetionat; Pentamidin-diisetionát; Pentamidin-diizetionát; Pentamidine Diisetionate; Pentamidine, diisétionate de; Pentamidine Isethionate (USAN); Pentamidine, Isétionate de; Pentamidini diisetionas; Pentamidini Isethionas; Pentamidini Isetionas; Pentamidino diizetionatas; Pentamidyny diizetionian; Пентамидина Изетионат.

4,4′-(Pentamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).

$C_{19}H_{24}N_4O_2,2C_2H_6O_4S$=592.7

CAS — 100-33-4 (pentamidine); 140-64-7 (pentamidine isetionate).
ATC — P01CX01.
UNII — V2P3K60DA2.

Pharmacopoeias. In *Eur.* (see p. vii), *Int*, and *US.*

Ph. Eur. 8: (Pentamidine Diisetionate; Pentamidine Isetionate BP 2014). A white or almost white powder or colourless crystals; it is hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers.

USP 36: (Pentamidine Isethionate). A white or almost white powder or colourless crystals. It is hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% carbon dioxide-free aqueous solution has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Immediate precipitation occurred when a solution of pentamidine isetionate 3 mg/mL in glucose 5% was mixed with each of 5 cephalosporin and 1 cephamycin injections.[1]

Pentamidine isetionate is reported to be incompatible with foscarnet.

1. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53**: 1461–2.

Pentamidine Mesilate *(BANM, rINNM)*

Mesilato de pentamidina; Pentamidina, mesilato de; Pentamidine Dimethylsulphonate; Pentamidine, Mésilate de; Pentamidine Mesylate; Pentamidine Methanesulphonate; Pentamidini Mesilas; RP-2512; Пентамидина Мезилат.

Pentamidine dimethanesulphonate.

$C_{19}H_{24}N_4O_2,2CH_3SO_3H$=532.6

CAS — 6823-79-6.
UNII — 863QB84D0A.

Pharmacopoeias. In *Int.*

Uses and Administration

Pentamidine, an aromatic diamidine derivative, is an antiprotozoal thought to act by several mechanisms, including interference with protozoal DNA and folate transformation and by inhibition of RNA and protein synthesis. It is used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma brucei gambiense* infections, in some forms of leishmaniasis, and in the treatment and prophylaxis of pneumocystis pneumonia. Pentamidine has also been tried in other protozoal infections including *Acanthamoeba* infection and babesiosis. For further information on these diseases see below.

Pentamidine has been given as the isetionate or mesilate salt. It was registered in 1950 as the mesilate, but had been used in protozoal diseases before this. The drug was re-evaluated and commercialised as the isetionate salt in 1984; this form is the one now available in most countries. Pentamidine isetionate 4 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base; pentamidine mesilate 3.6 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base.

Pentamidine isetionate is given by deep intramuscular injection or by slow intravenous infusion over at least 60 minutes; direct intravenous injection must be avoided. Patients should be lying down. The mesilate has usually been given intramuscularly.

In the treatment of early **African trypanosomiasis** due to *T. b. gambiense*, pentamidine isetionate 4 mg/kg may be given daily or on alternate days by intramuscular injection or intravenous infusion to a total of 7 to 10 doses. Pentamidine is not effective in trypanosomiasis with CNS involvement.

In the treatment of *visceral* **leishmaniasis**, and of *mucocutaneous* leishmaniasis due to *Leishmania braziliensis* or *L. aethiopica* that have not responded to antimonials, pentamidine isetionate 4 mg/kg may be given, by intravenous infusion or intramuscular injection three times weekly, for 5 to 25 weeks or longer. An alternative regimen in visceral leishmaniasis is to give 3 to 4 mg/kg, preferably by intramuscular injection, on alternate days to a maximum of 10 injections; the course may need to be repeated. In *cutaneous* leishmaniasis due to *L. aethiopica* or *L. guyanensis*, pentamidine isetionate 3 to 4 mg/kg may be given, preferably intramuscularly once or twice weekly, until the condition resolves. A weekly dose of 3 to 4 mg/kg is also used for diffuse cutaneous leishmaniasis due to *L. aethiopica* and should be continued for at least 4 months after parasites are no longer detectable on skin smears.

In the treatment of **pneumocystis pneumonia**, pentamidine isetionate 4 mg/kg is given once daily for 14 days or longer, by intramuscular injection or preferably slow intravenous infusion. Pentamidine isetionate is given by inhalation through a nebuliser to prevent pneumocystis pneumonia in HIV-positive patients in a dose of 300 mg once every 4 weeks; in those who cannot tolerate this dose 150 mg every 2 weeks may be used. It has also occasionally been used by this route for treating mild to moderate *P. jirovecii* infection in a dose of 600 mg daily for 3 weeks. Nebuliser design can affect the droplet size delivered and hence the amount of pentamidine reaching sites of action within the lungs. The optimal particle size is 1 to 2 micrometres. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to the drug.

Administration in children. The indications for use and doses of pentamidine in infants and children are the same as those for adults, see above.

Administration in renal impairment. Since renal clearance accounts for only a small proportion of pentamidine elimination, dosage adjustment is not generally considered necessary for mild to moderate degrees of renal impairment. UK licensed product information recommends dosage reductions in patients with pneumocystis pneumonia who have a creatinine clearance of less than 10 mL/minute. In patients with life-threatening disease the recommended dose of 4 mg/kg daily should be given for 7 to 10 days and then on alternate days for the remainder of the 14-dose course. In less severe disease the suggested dose is 4 mg/kg on alternate days for 14 doses.

Amoebic infections. *ACANTHAMOEBA INFECTIONS.* There have been a few case reports of intravenous pentamidine being used successfully to treat disseminated *Acanthamoeba* infection (p. 920.1) without evidence of CNS involvement in immunocompromised patients.[1,2] It is unlikely that pentamidine would be effective in infections involving the CNS.

1. Slater CA, *et al.* Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; 331: 85–7.
2. Murakawa GJ, *et al.* Disseminated Acanthamoeba in patients with AIDS: a report of five cases and a review of the literature. *Arch Dermatol* 1995; 131: 1291–6.

Babesiosis. Pentamidine has been tried for babesiosis (p. 920.2), but while some patients showed clinical improvements,[1-3] the efficacy and safety of pentamidine in this infection has been questioned.[4]

1. Francioli FB, *et al.* Response of babesiosis to pentamidine therapy. *Ann Intern Med* 1981; 94: 326–30.
2. Raoult D, *et al.* Babesiosis, pentamidine, and cotrimoxazole. *Ann Intern Med* 1987; 107: 944.
3. Clarke CS, *et al.* Babesiosis: under-reporting or case-clustering? *Postgrad Med J* 1989; 65: 591–3.
4. Teutsch SM, Juranek DD. Babesiosis. *Ann Intern Med* 1981; 95: 241.

Leishmaniasis. Pentamidine has been used in the treatment of **visceral** leishmaniasis (p. 923.1) in patients who have failed to respond to antimonials alone.[1] It has also been suggested as an alternative for long-term secondary prophylaxis in patients with HIV infection.[2]

A systematic review and meta-analysis[3] to determine the best drug management in the treatment of **cutaneous** leishmaniasis (p. 922.1) in Latin America reported similar cure rates for pentamidine and the pentavalent antimonials. Pentamidine has been extensively used and studied in French Guyana, where *L. guyanensis* causes most disease and cure rates higher than 90% have been reported after 2 doses of pentamidine. Pentamidine may be considered for treatment of patients with recurrent disease and was found to be superior to re-treatment with pentavalent antimonials in those who failed the treatment with the latter.[3] A short course of intramuscular pentamidine (3 to 4 mg/kg initially and repeated once 2 days later) was successful in treating 2 patients with Old World cutaneous leishmaniasis resistant to initial treatment with pentavalent antimonials or oral fluconazole.[4] A 73% cure rate was reported in 11 patients infected with *L. infantum*, *L. major*, or *L. tropica*.[5]

Diffuse cutaneous or **mucocutaneous** disease (p. 923.1) which is unresponsive to antimonials may respond to pentamidine.[1]

For mention of the use of pentamidine with paromomycin to treat visceral leishmaniasis in an HIV-infected patient, see p. 944.1.

1. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 15/04/09)
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 17/09/13)
3. Tuon FF, *et al.* Treatment of New World cutaneous leishmaniasis–a systematic review with a meta-analysis. *Int J Dermatol* 2008; 47: 109–24.
4. Jauréguiberry S, *et al.* Efficacy of short-course intramuscular pentamidine isethionate treatment on Old World localized cutaneous leishmaniasis in 2 patients. *Clin Infect Dis* 2006; 42: 1812–13.
5. Hellier I, *et al.* Treatment of Old World cutaneous leishmaniasis by pentamidine isethionate: an open study of 11 patients. *Dermatology* 2000; 200: 120–3.

Pneumocystis pneumonia. In the treatment of pneumocystis pneumonia (p. 567.2) intravenous pentamidine is generally reserved for patients with moderate to severe disease who do not respond to, or cannot tolerate, co-trimoxazole. Co-trimoxazole with pentamidine is no more effective than pentamidine alone in these patients and is potentially more toxic than either drug.[1] Inhaled pentamidine has occasionally been suggested for mild to moderate infection, but is now generally only used for prophylaxis. However, patients given inhaled pentamidine may be prone to extrapulmonary *Pneumocystis* infections.[2,3]

In both primary and secondary **prophylaxis** of pneumocystis pneumonia in immunocompromised patients, co-trimoxazole is preferred to inhaled pentamidine. Comparative studies have shown that, in the short term, inhaled pentamidine has been less effective than co-trimoxazole[4,5] and no more effective than another common prophylactic drug, dapsone.[6,7] In addition, both co-trimoxazole and dapsone (given with pyrimethamine) also provide protection against toxoplasmosis and extrapulmonary pneumocystis infections. However, inhaled pentamidine is better tolerated than either of these, and studies have suggested that in the long term the efficacy of the three drugs is comparable,[8,9] at least in patients with CD4+ T lymphocyte counts of more than 100 cells/microlitre. Increasing the dose of pentamidine from 300 mg every four weeks to 300 mg every two weeks[10,11] or 600 mg every week[12] may improve efficacy further. Intermittent parenteral dosage of pentamidine has been used when the more usual drugs cannot be given.[13]

1. Glatt AE, Chirgwin K. Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Arch Intern Med* 1990; 150: 271–9.
2. Witt K, *et al.* Dissemination of Pneumocystis carinii in patients with AIDS. *Scand J Infect Dis* 1991; 23: 691–5.
3. Sha BE, *et al.* Pneumocystis carinii choroiditis in patients with AIDS: clinical features, response to therapy, and outcome. *J Acquir Immune Defic Syndr Hum Retrovirol* 1992; 5: 1051–8.
4. Schneider MME, *et al.* A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992; 327: 1836–41.
5. Hardy WD, *et al.* A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992; 327: 1842–8.
6. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; 328: 1514–20.
7. Torres RA, *et al.* Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Am J Med* 1993; 95: 573–83.
8. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; 332: 693–9.
9. Rizzardi GP, *et al.* Risks and benefits of aerosolized pentamidine and cotrimoxazole in primary prophylaxis of Pneumocystis carinii pneumonia in HIV-1-infected patients: a two-year Italian multicentric randomized controlled trial. *J Infect* 1996; 32: 123–31.
10. Kronawitter U, *et al.* Low incidence of Pneumocystis carinii pneumonia in HIV patients receiving 300 mg pentamidine aerosol every 2 weeks. *Clin Investig* 1992; 70: 1089–91.
11. Rizzardi GP, *et al.* Better efficacy of twice-monthly than monthly aerosolised pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with AIDS: an Italian multicentric randomised controlled trial. *J Infect* 1995; 31: 99–105.
12. Ong RLC, *et al.* Efficacy and effects on pulmonary function tests of weekly 600 mg aerosol pentamidine as prophylaxis against Pneumocystis carinii pneumonia. *Infection* 1992; 20: 136–9.
13. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58 (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 12/04/09)

African trypanosomiasis. Pentamidine is used for the early or haematolymphatic phase of African trypanosomiasis caused by *Trypanosoma brucei gambiense* (p. 925.2).[1] It is reported to be less effective against *T. b. rhodesiense* and in some areas resistance of *T. b. gambiense* to pentamidine is increasing. Pentamidine has been used with suramin for *T. b. gambiense* infections but this has not been shown to be clinically superior to pentamidine alone.[2]

1. WHO. Control and surveillance of African trypanosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 881* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_881.pdf (accessed 27/07/09)
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; 90: 183–6.

Adverse Effects

Pentamidine is a toxic drug and adverse effects are frequent and sometimes severe when given parenterally; toxicity is more common in patients with AIDS. Fatalities due to severe hypotension, hypoglycaemia, acute pancreatitis, and cardiac arrhythmias have been reported.

Rapid intravenous injection has resulted in sudden hypotension and immediate reactions such as flushing, dizziness, headache, vomiting, breathlessness, tachycardia, and fainting. Hypotension may also occur when pentamidine is given intramuscularly or by slow intravenous infusion. Pentamidine may prolong the QT interval and isolated cases of torsade de pointes have been reported. Renal impairment is common (over 20% of patients), usually manifesting as mild and reversible raised blood urea nitrogen and serum creatinine concentrations, but acute renal failure can occur. Hypoglycaemia, sometimes followed by hyperglycaemia and type 1 diabetes mellitus, is well documented. Other severe adverse effects include leucopenia, thrombocytopenia, and hypocalcaemia; possible Stevens-Johnson syndrome has also been reported. Less severe adverse effects include azotaemia, raised liver enzyme values, anaemia, macroscopic haematuria, hypomagnesaemia, hyperkalaemia, nausea and vomiting, rashes, and taste disturbances. Rhabdomyolysis has been rarely reported after intramuscular use. Intramuscular pentamidine often causes pain, swelling, sterile abscess formation, and tissue necrosis at the site of injection. Similar damage can follow extravasation during intravenous dosage.

Pentamidine is not as toxic when given by inhalation for the prophylaxis of pneumocystis pneumonia. The commonest adverse effects with this route are cough and bronchoconstriction (particularly in patients with a history of smoking or asthma) and may be controlled by a bronchodilator. Inhalation may leave a bitter taste. Pneumothorax has been reported, but may be associated with the disease. There have been rare reports of adverse effects such as those seen when pentamidine is given by injection.

Incidence of adverse effects. Adverse effects were seen in 46.8% of 404 patients given pentamidine parenterally for the treatment of pneumocystis pneumonia, according to an analysis from the CDC in the USA.[1] The reactions included impaired renal function (23.5% of patients),

abnormal liver function (9.6%), hypoglycaemia (6.2%), haematological disturbances (4.2%), rashes (1.5%), and hypocalcaemia (1.2%). Local reactions at injection sites such as pain and abscess occurred in 18.3% and immediate adverse effects such as hypotension in 9.6%.

Retrospective studies[2-4] suggest that adverse reactions occur more commonly in patients with AIDS.

An evaluation of pentamidine in the treatment of 82 patients with visceral leishmaniasis further illustrates its toxicity.[5] Cardiotoxicity (tachycardia, hypotension, and ECG changes of non-specific myocarditis), occurred in about 23% of patients. No hypoglycaemic reaction was noted, but 4 patients developed diabetes mellitus and 3 of them were found to be insulin-dependent. Other adverse reactions included gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain, or diarrhoea) in about 78%, CNS effects (headache associated with flushing, delirium, or sensory disturbances resembling pins and needles [paraesthesias]) in about 24%, mild reversible albuminuria in about 7%, and allergic manifestations (generalised urticaria, itching, and conjunctival congestion) in about 5%. One patient had severe anaphylaxis.

1. Walzer PD, *et al.* Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; 80: 83–93.
2. Lachaal M, Venuto RC. Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. *Am J Med* 1989; 87: 260–3.
3. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; 25: 1171–4.
4. O'Brien JG, *et al.* A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; 24: 854–9.
5. Jha TK. Evaluation of diamidine compound (pentamidine isethionate) in the treatment of resistant cases of kala-azar occurring in North Bihar, India. *Trans R Soc Trop Med Hyg* 1983; 77: 167–70.

Effects on the blood. Haemolytic anaemia has been reported in a 55-year-old man with AIDS being treated with intravenous pentamidine for pneumocystis pneumonia. Symptoms developed after a cumulative dose of 3740 mg of pentamidine had been given and resolved several days after stopping the pentamidine.[1] Megaloblastic anaemia after intravenous pentamidine has also been reported.[2]

1. Taguchi H, *et al.* Pentamidine-induced hemolytic anemia in an AIDS patient. *Ann Pharmacother* 1999; 33: 503.
2. Au WY, *et al.* Intravenous pentamidine induced megaloblastic anaemia. *Haematologica* 2002; 87: ECR06.

Effects on carbohydrate metabolism. As reported under Incidence of Adverse Effects, p. 945.3, pentamidine can have a range of effects on carbohydrate metabolism. Four patients receiving pentamidine for pneumocystis pneumonia developed severe fasting hypoglycaemia followed later by hyperglycaemia and type 1 diabetes mellitus.[1] It has been suggested that pentamidine has a toxic effect on the β-cells of the pancreatic islets and can induce an early cytolytic release of insulin and hypoglycaemia, followed by β-cell destruction, insulin deficiency, and diabetes mellitus.[1,2] AIDS patients appear to be highly susceptible and have a higher incidence of hypoglycaemia due to pentamidine.[3] The action on the pancreas has led to fatal acute *pancreatitis*;[4-6] fatal hypoglycaemia has also been reported.[7] These reports[1-5,7] involved pentamidine given by injection; pancreatitis[8,9] and diabetes mellitus[10,11] have also been reported in patients given pentamidine by aerosol inhalation.

1. Bouchard P, *et al.* Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes* 1982; 31: 40–5.
2. Osei K, *et al.* Diabetogenic effect of pentamidine: in vitro and in vivo studies in a patient with malignant insulinoma. *Am J Med* 1984; 77: 41–6.
3. Stahl-Bayliss CM, *et al.* Pentamidine-induced hypoglycemia in patients with the acquired immune deficiency syndrome. *Clin Pharmacol Ther* 1986; 39: 271–5.
4. Salmeron S, *et al.* Pentamidine and pancreatitis. *Ann Intern Med* 1986; 105: 140–1.
5. Zuger A, *et al.* Pentamidine-associated fatal acute pancreatitis. *JAMA* 1986; 256: 2383–5.
6. Sauleda J, *et al.* Probable pentamidine-induced acute pancreatitis. *Ann Pharmacother* 1994; 28: 52–3.
7. Sattler FR, Waskin H. Pentamidine and fatal hypoglycemia. *Ann Intern Med* 1987; 107: 789–90.
8. Herer B, *et al.* Pancreatitis associated with pentamidine by aerosol. *BMJ* 1989; 298: 605.
9. Hart CC. Aerosolized pentamidine and pancreatitis. *Ann Intern Med* 1989; 111: 691.
10. Fisch A. Diabetes mellitus in a patient with AIDS after treatment with pentamidine aerosol. *BMJ* 1990; 301: 875.
11. Chen JP, *et al.* Diabetes after aerosolized pentamidine. *Ann Intern Med* 1991; 114: 913–14.

Effects on the cardiovascular system. *Hypotension* is a problem with intravenous pentamidine, but can be reduced by infusing the dose over 60 minutes, when the incidence of hypotension appears to be similar to that with the intramuscular route.[1,2] Intravenous pentamidine has also been associated with *torsade de pointes*,[3-6] *Sinus bradycardia* and second-degree *heart block* has been described in an HIV-positive patient treated with intravenous pentamidine for pneumocystis pneumonia.[7]

1. Navin TR, Fontaine RE. Intravenous versus intramuscular administration of pentamidine. *N Engl J Med* 1984; 311: 1701.
2. Helmick CG, Green JK. Pentamidine-associated hypotension and route of administration. *Ann Intern Med* 1985; 103: 480.
3. Harel Y, *et al.* Pentamidine-induced torsade de pointes. *Pediatr Infect Dis J* 1993; 12: 692–4.
4. Miller HC. Cardiac arrest after intravenous pentamidine in an infant. *Pediatr Infect Dis J* 1993; 12: 694–6.
5. Zanetti LAF, Oliphant CM. Pentamidine-induced torsade de pointes. *Ann Pharmacother* 1994; 28: 282–3.
6. Otsuka M, *et al.* Torsades de pointes complicating pentamidine therapy of Pneumocystis carinii pneumonia in acute myelogenous leukemia. *Intern Med* 1997; 36: 705–8.
7. Antoniou T, Gough KA. Early-onset pentamidine-associated second-degree heart block and sinus bradycardia: case report and review of the literature. *Pharmacotherapy* 2005; 25: 899–903.

Effects on the kidneys. In an analysis[1] of the adverse effects of parenteral pentamidine (see also under Incidence of Adverse Effects p. 945.3), nephrotoxicity was often the most serious adverse reaction, although it was impossible to attribute it solely to pentamidine. Severe renal impairment occurred in 15 of 404 patients and contributed materially to 12 of 14 ensuing deaths. However, elevation of blood urea nitrogen was usually relatively mild and reversible in those patients who had normal pretreatment renal function and had received no other nephrotoxic agents. In two studies in patients with AIDS,[2,3] severe nephrotoxicity (increase in serum creatinine concentration of 500 micrograms per 100 mL) was reported in about 40% of patients. Analysis of risk factors suggested that the development of adverse reactions to parenteral pentamidine is correlated with the total dose received and the duration of treatment,[2,3] but not with the initial degree of renal function.[2] It has been noted that renal toxicity is more common when pentamidine is given intramuscularly, rather than intravenously, to AIDS patients with diarrhoea, suggesting that fluid status might have an important role.[4] There have been instances of renal failure occurring when pentamidine is inhaled as an aerosol for its local effect.[5,6]

1. Walzer PD, *et al.* Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; 80: 83–93.
2. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; 25: 1171–4.
3. O'Brien JG, *et al.* A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; 24: 854–9.
4. Stehr-Green JK, Helmick CG. Pentamidine and renal toxicity. *N Engl J Med* 1985; 313: 694–5.
5. Miller RF, *et al.* Acute renal failure after nebulised pentamidine. *Lancet* 1989; i: 1271–2.
6. Chapelon C, *et al.* Renal insufficiency with nebulised pentamidine. *Lancet* 1989; ii: 1045–6.

Effects on the nervous system. Paraesthesias, including perioral paraesthesias,[1,2] have been reported with pentamidine therapy. Perioral numbness occurred in a patient soon after starting the third intravenous infusion of pentamidine for treatment of pneumocystis pneumonia and disappeared after the end of the infusion; numbness recurred with all subsequent pentamidine infusions.[1]

See also under Incidence, p. 945.3.

1. Milligan KS, Phillips DL. Perioral numbness associated with intravenous pentamidine administration. *Ann Pharmacother* 2007; 41: 153–6.
2. Brown E, *et al.* Perioral and facial parasthesias associated with intravenous pentamidine use for pneumocystis prophylaxis. *Pediatr Hematol Oncol* 2010; 27: 658–60.

Effects on the respiratory system. Although inhaled pentamidine has produced reactions that are normally associated with the parenteral route, the main problem after inhalation is bronchoconstriction;[1] it can be prevented by prior use of a bronchodilator. Acute eosinophilic pneumonia associated with nebulised pentamidine has been reported in a patient.[2] Concern has also been expressed at the risks to those who are with the patient at the time of inhalation and are exposed to nebulised pentamidine.[3-5]

1. Smith DE, *et al.* Reversible bronchoconstriction with nebulised pentamidine. *Lancet* 1988; ii: 905.
2. Dupon M, *et al.* Acute eosinophilic pneumonia induced by inhaled pentamidine isethionate. *BMJ* 1993; 306: 109.
3. McDiarmid MA, Jacobson-Kram D. Aerosolised pentamidine and public health. *Lancet* 1989; ii: 863–4.
4. Thomas SHL, *et al.* Aerosolised pentamidine. *Lancet* 1989; ii: 1284.
5. Smaldone GC, *et al.* Detection of inhaled pentamidine in health care workers. *N Engl J Med* 1991; 325: 891–2.

Effects on the skin. Toxic epidermal necrolysis occurred in a man with SLE the day after being given aerosolised pentamidine for the prophylaxis of pneumocystis pneumonia. A lymphocyte stimulating test was performed on all candidate drugs, and was positive for pentamidine. Treatment with pentamidine was stopped and the patient was given plasma exchange, corticosteroids, and normal immunoglobulin. The eruption slowly resolved over 3 to 4 weeks.[1]

1. Watarai A, *et al.* Toxic epidermal necrolysis caused by aerosolized pentamidine. *Am J Med* 2009; 122: e1–e2.

Precautions

Pentamidine should be used under close supervision and great care is necessary if it is used in patients suffering from any condition likely to be exacerbated by its adverse effects. The CSF should be checked for signs of CNS involvement before giving pentamidine for trypanosomiasis, since it is unlikely to be effective in such cases. Patients should be lying down while it is given and their blood pressure should be monitored. Kidney and liver function, blood-glucose concentrations, blood and platelet counts, and other parameters indicative of developing toxicity, such as serum-calcium, -magnesium, and -potassium concentrations and the ECG, should also be assessed regularly during courses of treatment with pentamidine. Particular caution and continuous cardiac monitoring is advised if the patient's QT interval exceeds 500 milliseconds while receiving treatment; alternative regimens should be used if the QT interval exceeds 550 milliseconds.

Patients with a history of asthma or smoking may be at increased risk of cough and bronchospasm during inhalation of nebulised pentamidine. Symptoms may be controlled by giving a bronchodilator before pentamidine. Pentamidine solution should not be mixed with other drugs nor should a bronchodilator be given in the same nebuliser. Extrapulmonary *Pneumocystis jirovecii* infections may occur in patients given nebulised pentamidine and should be considered in patients with unexplained signs and symptoms. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to pentamidine.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pentamidine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

Use of pentamidine with other nephrotoxic drugs such as amphotericin B or foscarnet should preferably be avoided. Extreme caution is also necessary if pentamidine is given with other drugs, such as foscarnet, that can cause hypocalcaemia. There is an increased risk of ventricular arrhythmias if pentamidine is given with drugs which prolong the QT interval such as intravenous erythromycin, fluoroquinolones, amiodarone, tricyclic antidepressants, phenothiazines, or terfenadine. There may be an increased risk of pancreatitis when intravenous pentamidine is used with didanosine, stavudine, or zalcitabine and such combinations should be avoided. Pentamidine is structurally similar to amiloride and therefore use with potassium-sparing diuretics may result in severe hyperkalaemia.

Pharmacokinetics

After parenteral doses of the isetionate, pentamidine is widely distributed in the body. During repeated dosing accumulation is believed to occur, particularly in the liver and kidneys. After intravenous injection plasma concentrations fall rapidly to one twentieth of peak values during the first 2 hours, followed by a much slower decline thereafter. On intramuscular injection peak concentrations occur after about 1 hour and the serum concentration remains the same for about 24 hours. The apparent volume of distribution of pentamidine after intramuscular injection is more than 3 times that seen after intravenous use. Elimination half-lives of 6 hours after intravenous infusion and 9 hours after intramuscular injection have been cited, but probably represent an intermediate value, and terminal elimination half-lives of between several days and weeks have been reported. After multiple intravenous doses the half-life was 12.5 days. Only a small amount is slowly excreted unchanged in the urine.

Distribution to the lung is relatively poor after injection. Systemic absorption after inhalation is reported to result in peak plasma concentrations of 5 to 10% of those after parenteral use, and there have been a few reports of systemic adverse effects. The half-life of aerosolised pentamidine in bronchial alveolar lavage fluid is more than 10 to 14 days. Particle or droplet size appears to be important in achieving adequate pulmonary distribution.

References.

1. O'Doherty MJ, *et al.* Differences in relative efficiency of nebulisers for pentamidine administration. *Lancet* 1988; ii: 1283–6.
2. Simonds AK, *et al.* Aerosolised pentamidine. *Lancet* 1989; i: 221–2.
3. Baskin ML, *et al.* Regional deposition of aerosolized pentamidine: effects of body position and breathing pattern. *Ann Intern Med* 1990; 113: 677–83.
4. Bronner U, *et al.* Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of Trypanosoma gambiense in Côte d'Ivoire. *Trans R Soc Trop Med Hyg* 1991; 85: 608–11.

5. Lidman C, *et al.* Plasma pentamidine concentrations vary between individuals with Pneumocystis carinii pneumonia and the drug is actively secreted by the kidney. *J Antimicrob Chemother* 1994; 33: 803–10.
6. Bronner U, *et al.* Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. *Br J Clin Pharmacol* 1995; 39: 289–95.
7. Conte JE, Golden JA. Intrapulmonary and systemic pharmacokinetics of aerosolized pentamidine used for prophylaxis of Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus. *J Clin Pharmacol* 1995; 35: 1166–73.

Renal impairment. In a study[1] of patients with normal renal function or on haemodialysis, renal clearance of pentamidine during the 24 hours after intravenous use was 2.1% of the plasma clearance in those with normal renal function, suggesting that pentamidine elimination would be largely unaffected by renal impairment. In those with end-stage renal disease on haemodialysis the terminal elimination half-life after a single dose was prolonged to about 75 hours, compared with 30 hours in the patients with normal renal function, but the volumes of distribution and area under the concentration-time curve were not significantly different. In patients with normal or mildly impaired renal function who had received between 12 and 21 doses, the terminal elimination half-life after the final dose was about 12 days and pentamidine was still detectable in the plasma after 6 weeks. There was evidence of accumulation of pentamidine during repeated daily dosing.

1. Conte JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. *J Infect Dis* 1991; 163: 169–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Pentacarinat; *Braz.*: Pentacarinat; *Fr.*: Pentacarinat; *Ger.*: Pentacarinat; *Gr.*: Pentacarinat; Pentam; *Hong Kong*: Pentacarinat; *Irl.*: Pentacarinat†; *Ital.*: Pentacarinat; *Neth.*: Pentacarinat; *NZ*: Pentacarinat; *Port.*: Pentamina†; *Spain*: Pentacarinat; *Swed.*: Pentacarinat; *Switz.*: Pentacarinat; *Thai.*: Pentacarinat; *UK*: Pentacarinat; *USA*: NebuPent; Pentacarinat; Pentam.

Pharmacopoeial Preparations
BP 2014: Pentamidine Injection.

Quinfamide *(USAN, rINN)*

Quinfamida; Quinfamidum; Win-40014; Хинфамид.
1-(Dichloroacetyl)-1,2,3,4-tetrahydroquinolin-6-ol 2-furoic acid ester.
$C_{16}H_{13}Cl_2NO_4$=354.2
CAS — 62265-68-3.
UNII — O1ZB1046R1.

Profile

Quinfamide is a luminal amoebicide. It is given orally for intestinal amoebiasis in a dose of 300 mg, either as a single dose or as three divided doses over 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Amefin; Amefurt†; Amenox; Amofarma; Amofurt†; Bisidim; Celemin†; Doffler; Falacid†; Luminovag; Protosin; Quocel; Serphamida.

Multi-ingredient Preparations. *Mex.*: Amoebriz; Bensolmin Complex; Farmiver; Oxal; Vermox-Plus.

Robenidine Hydrochloride

(BANM, USAN, rINNM)

CL-78116; Hidrocloruro de robenidina; Robenidina, hidrocloruro de; Robénidine, Chlorhydrate de; Robenidini Hydrochloridum; Robenzidene Hydrochloride; Робенидина Гидрохлорид.
1,3-Bis(4-chlorobenzylideneamino)guanidine hydrochloride.
$C_{15}H_{13}Cl_2N_5$,HCl=370.7
CAS — 25875-51-8 (robenidine); 25875-50-7 (robenidine hydrochloride).
UNII — 8STT15Y392.

Profile

Robenidine is an antiprotozoal used as the hydrochloride in veterinary practice for the prevention of coccidiosis in poultry and rabbits.

Ronidazole *(BAN, USAN, pINN)*

Ronidazol; Ronidazolum; Ронидазол.
(1-Methyl-5-nitroimidazol-2-yl)methyl carbamate.
$C_6H_8N_4O_4$=200.2
CAS — 7681-76-7.
ATC Vet — QP51AA08.
UNII — E01R4M1063.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Ronidazole). A white to yellowish-brown, odourless or almost odourless powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Protect from light.

Profile

Ronidazole is a 5-nitroimidazole antiprotozoal that is used in veterinary practice for the control of trichomoniasis in cage birds and pigeons. It has also been added to turkey feeding stuffs and has been used for the control of swine dysentery. Ronidazole is considered to be carcinogenic and its use in food-producing animals has been banned in some countries.

Salinomycin Sodium *(BANM, rINNM)*

AHR-3096 (salinomycin); K-364 (salinomycin); K-748364A (salinomycin); Natrii Salinomycinum; Salinomicina sódica; Salinomycine Sodique; Натрий Салиномицин.
Sodium (2*R*)-2-[(2*R*,5*S*,6*R*)-6-[[1*S*,2*S*,3*S*,5*R*)-5-[(2*S*,5*S*,7*R*,9*S*,10*S*,12*R*,15*R*)-2-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl]-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-5-methylpyran-2-yl] butyrate.
$C_{42}H_{69}NaO_{11}$=773.0
CAS — 53003-10-4 (salinomycin); 55721-31-8 (salinomycin sodium).
UNII — 92UOD3BMEK.

Profile

Salinomycin, an ionophore antibiotic produced by *Streptomyces albus*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor in pigs.

Poisoning. Ionophore antibacterials selectively bind certain ions causing intra- and extracellular biochemical disturbances. Salinomycin preferentially binds to potassium and interferes with potassium transport across mitochondrial membranes; the sodium/calcium ion exchange mechanism may also be disrupted. It also has potent sympathomimetic effects. Animal poisonings with ionophore antibacterials have been reported, with skeletal muscle in all animals and cardiac muscle in some animals being affected.[1] In humans, prolonged rhabdomyolysis (40 days), pain, and disability were reported in a healthy man after he accidentally inhaled and swallowed about 1 mg/kg of salinomycin. Supportive treatment (with activated charcoal, oxygen, and intravenous fluids) is recommended, as well as aggressive management of myoglobinuria (with urinary alkalinisation) and prolonged bed rest to reduce metabolic demand on the muscle; an early baseline cardiac ECG is also recommended.[1]

1. Story P, Doube A. A case of human poisoning by salinomycin, an agricultural antibiotic. *N Z Med J* 2004; 117: U799.

Satranidazole *(rINN)*

C 10213-Go; CG-10213-Go; Go-10213; Satranidazol; Satranidazolum; Сатранидазол.
1-(1-Methyl-5-nitroimidazol-2-yl)-3-(methylsulfonyl)-2-imidazolidinone.
$C_8H_{11}N_5O_5S$=289.3
CAS — 56302-13-7.
UNII — 4N7G8A6439.

Profile

Satranidazole is a 5-nitroimidazole derivative with properties similar to those of metronidazole (p. 936.1). It is used in the treatment of amoebiasis, giardiasis, and trichomoniasis.

References.
1. Muzaffar J, *et al.* Randomized, single-blind, placebo-controlled multicenter trial to compare the efficacy and safety of metronidazole and satranidazole in patients with amebic liver abscess. *Dig Dis Sci* 2006; 51: 2270–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Satrogyl; Satromax.

Multi-ingredient Preparations. *India*: Satrogyl-O; Satromax-O.

Secnidazole *(BAN, rINN)*

PM-185184; 14539-RP; RP-14539; Secnidazol; Secnidazolum; Seknidazol; Секнидазол.
1-(2-Methyl-5-nitroimidazol-1-yl)propan-2-ol.
$C_7H_{11}N_3O_3$=185.2
CAS — 3366-95-8.
ATC — P01AB07.
UNII — R3459K699K.

Profile

Secnidazole is a 5-nitroimidazole derivative with properties similar to those of metronidazole (p. 936.1), apart from a much longer plasma half-life of 20 hours or more. It is used in the treatment of amoebiasis, giardiasis, and trichomoniasis.

For the treatment of intestinal amoebiasis and trichomoniasis in adults, secnidazole is given orally, usually as a single dose of 2 g; for hepatic amoebiasis an oral dose of 1.5 g daily is given in single or divided doses for 5 days. For the treatment of intestinal amoebiasis and giardiasis in children 30 mg/kg may be given as a single oral dose; in hepatic amoebiasis an oral dose of 30 mg/kg daily is given in single or divided doses for 5 days.

References.
1. Gillis JC, Wiseman LR. Secnidazole: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. *Drugs* 1996; 51: 621–38.
2. Girginkardeşler N, *et al. Dientamoeba fragilis*, a neglected cause of diarrhea, successfully treated with secnidazole. *Clin Microbiol Infect* 2003; 9: 110–13.
3. Escobedo AA, *et al.* A randomized trial comparing mebendazole and secnidazole for the treatment of giardiasis. *Ann Trop Med Parasitol* 2003; 97: 499–504.
4. Núñez JT, Gómez G. Low-dose secnidazole in the treatment of bacterial vaginosis. *Int J Gynaecol Obstet* 2005; 88: 281–5.
5. Slim R, *et al.* Secnidazole-induced acute pancreatitis: a new side-effect for an old drug? *JOP* 2010; 11: 85–6.
6. Bohbot J-M, *et al.* Treatment of bacterial vaginosis: a multicenter, double-blind, double-dummy, randomised phase III study comparing secnidazole and metronidazole. *Infect Dis Obstet Gynecol* 2010; 2010: 705692.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flagentyl; *Braz.*: Deprozol; Neodazol; Secfar; Secnal; Secnaxidol; Secni-Plus; Secnics; Secnidal; Secnidalin; Secnihexal; Secnitec; Secnix; Secnizol; Sectil; Tecnid; Unigyn; *China*: Ke Ni (可尼); Kelisaike (可立塞克); *Ming Jie* (明捷); *Sai Ta Le* (赛他乐); *Sha Ba Ke* (沙巴克); Xi Ni Di (西尼迪); Xin Shuang (信爽); You Ke Xin (优克欣); *Fr.*: Secnol; *India*: Ambiform; Amitab; Entosec; Etisec; Flagentyl; Noameba-DS†; Secnil; *Indon.*: Sentyl†; *Mex.*: Conamvag; Gisistin; Minovag; Sabima; Secnidal; *Philipp.*: Flagentyl; *Port.*: Flagentyl; *Rus.*: Tagera (Тагера); *Turk.*: Flagentyl; *Ukr.*: Secnidox (Секнидокс); *Venez.*: Ambese; Daksol; Fazol; Secnidal; Secnivax; Seczol; Unidazol.

Multi-ingredient Preparations. *Arg.*: Gynerium UD; Gynerium; *Braz.*: Gynopac; *India*: Azintra-3; Azithral XP; Eradikit; Eve Kit; Fas-3 Kit; FC-Kit; Fiscon Tab; Flunec Combikit; Fulkit; Fygek-AS; Gyn-3; Gynotrim Kit; Hif-AS; Kit-3D; Od-Kit; Saf Kit; *Mex.*: C Cobistal; Gitrasek; Sepia; Sporasec; *Rus.*: Safocid (Сафоцид); *Ukr.*: Ginekit (Гинекит); *Venez.*: Sporasec.

Semduramicin *(BAN, USAN, rINN)*

Semduramicina; Semduramicine; Semduramicinum; UK-61689-2 (semduramicin sodium); UK-61689; Семдурамицин.
(2*R*,3*S*,4*S*,5*R*,6*S*)-Tetrahydro-2,4-dihydroxy-6-[(*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)-9-hydroxy-2,8-dimethyl-2-[(2*S*,2′*R*,3′*S*,5′*R*)-octahydro-2-methyl-5′-[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-3′-[(2*S*,5*S*,6*R*)-tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy]-2,2′-bifuran-5-yl]-1,6-dioxaspiro[4.5]dec-7-yl]ethyl]-5-methoxy-3-methyl-2*H*-pyran-2-ylacetic acid.
$C_{45}H_{76}O_{16}$=873.1
CAS — 113378-31-7 (semduramicin); 119068-77-8 (semduramicin sodium).
UNII — P6VXL377WL.

Profile

Semduramicin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry. It is also used as the sodium salt.

Suramin Sodium *(rINN)*

Antrypol; Bayer-205; CI-1003; Fourneau-309; Naganinum; Naganol; NSC-34936; Suramin Hexasodium (USAN); Suramina sódica; Suramine Sodique; Suraminum Natricum; Сурамин Натрий.
The symmetrical 3″-urea of the sodium salt of 8-(3-benzamido-4-methylbenzamido)naphthalene-1,3,5-trisul-

The symbol † denotes a preparation no longer actively marketed

phonic acid; Hexasodium 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis(1,3,5-naphthalenetrisulfonate).
$C_{51}H_{34}N_6Na_6O_{23}S_6$=1429.2
CAS — 145-63-1 (suramin); 129-46-4 (suramin sodium).
ATC — P01CX02.
ATC Vet — QP51AE02.
UNII — 89521262IH.

Pharmacopoeias. In *Fr.*, *Int.*, and *It.*

Uses and Administration

Suramin is a trypanocide used in the treatment of African trypanosomiasis and as an anthelmintic in the treatment of onchocerciasis (see below).

Suramin is given as suramin sodium by slow intravenous injection, usually as a 10% solution. Because of the danger of severe reactions it is advisable to give a test dose before starting treatment.

In **African trypanosomiasis** suramin is used mainly for the early (haematolymphatic) stages of *Trypanosoma brucei rhodesiense* infection; pentamidine may be preferred for early-stage treatment of *T. b. gambiense* infection. Suramin is not used for late-stage infections with CNS involvement. Early-stage trypanosomiasis treatment begins with a (test) dose of 5 mg/kg of suramin on day 1. This is given with a pause of at least 1 minute after injecting the first few microlitres; the next 0.5 mL is given over 30 seconds with a wait of one minute before injecting the remainder of the dose over several minutes. If the test dose is tolerated 10 mg/kg is given on day 3, then 20 mg/kg on days 5, 11, 17, 23, and 30. Another schedule consists of a test dose of 100 to 200 mg and then 5 doses of 1 g given on days 1, 3, 7, 14, and 21.

For doses used in children, and in **onchocerciasis** see below.

General references.
1. McGeary RP, *et al.* Suramin: clinical uses and structure-activity relationships. *Mini Rev Med Chem* 2008; **8**: 1384–94.

Administration in children. For the treatment of early-stage African trypanosomiasis in children, suramin may be given by slow intravenous injection. A (test) dose of 5 mg/kg is given on day 1 (see above), 10 mg/kg on day 3, and 20 mg/kg on days 5, 11, 17, 23, and 30. Another schedule consists of a test dose of 100 to 200 mg and then 5 doses of 20 mg/kg given on days 1, 3, 7, 14, and 21.

Malignant neoplasms. Suramin is reported to have antineoplastic activity and has been studied in several malignant neoplasms, in particular hormone-resistant prostatic cancer (p. 712.3).[1-9] However, its clinical usefulness is hindered by dose-limiting toxicity and problems in developing a simple dose schedule. It has also been investigated as a chemosensitiser.[10-12]
1. Stein CA, *et al.* Suramin: an anticancer drug with a unique mechanism of action. *J Clin Oncol* 1989; **7**: 499–508.
2. Kilbourn RG. Suramin: new therapeutic concepts for an old drug. *Cancer Bull* 1991; **43**: 265–7.
3. Rapoport BL, *et al.* Suramin in combination with mitomycin C in hormone-resistant prostate cancer: a phase II clinical study. *Ann Oncol* 1993; **4**: 567–73.
4. Woll PJ, *et al.* Suramin for breast and prostate cancer: a pilot study of intermittent short infusions without adaptive controls. *Ann Oncol* 1994; **5**: 597–600.
5. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41**: 299–307.
6. Eisenberger MA, Reyno LM. Suramin. *Cancer Treat Rev* 1994; **20**: 259–73.
7. Rosen PJ, *et al.* Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. *J Clin Oncol* 1996; **14**: 1626–36.
8. Small EJ, *et al.* Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol* 2000; **18**: 1440–50.
9. Kaur M, *et al.* Suramin's development: what did we learn? *Invest New Drugs* 2002; **20**: 209–19.
10. Villalona-Calero MA, *et al.* Noncytotoxic suramin as a chemosensitizer in patients with advanced non-small-cell lung cancer: a phase II study. *Ann Oncol* 2008; **19**: 1903–9.
11. George S, *et al.* Phase I/II trial of 5-fluorouracil and a noncytotoxic dose level of suramin in patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2008; **6**: 79–85.
12. Lam ET, *et al.* Phase I trial of non-cytotoxic suramin as a modulator of docetaxel and gemcitabine therapy in previously treated patients with non-small cell lung cancer. *Cancer Chemother Pharmacol* 2010; **66**: 1019–29.

Onchocerciasis. Although suramin is the only drug in clinical use for onchocerciasis that is effective against adult worms, its use is restricted because of the frequency of associated complications and its intrinsic toxicity. Treatment of onchocerciasis (p. 147.2) is currently based on continuous suppression of microfilariae by regular use of ivermectin. WHO[1] advises that suramin should only be considered for the curative treatment of individuals in areas without transmission of onchocerciasis and of individuals leaving an endemic area, and for severe hyperreactive onchodermatitis where symptoms are not adequately controlled with ivermectin. WHO[2] also recommends that it should not be used to treat onchocerciasis in the elderly or infirm, in patients with severe liver or renal disease, in totally blind patients (unless they require relief from intensely itchy lesions), or in pregnant women (who should be treated after delivery).

A total dose of 66.7 mg/kg in six incremental weekly doses is recommended.[1,2] The first (test) dose of suramin sodium 3.3 mg/kg should be given very cautiously by slow intravenous injection; this is 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.[2]
1. WHO. Onchocerciasis and its control: report of a WHO expert committee. *WHO Tech Rep Ser 852* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_852.pdf (accessed 27/07/09)
2. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/04/09)

African trypanosomiasis. Suramin is used in the treatment of the early haematolymphatic phase of African trypanosomiasis (p. 925.2) caused by *Trypanosoma brucei rhodesiense* and for *T. b. gambiense* infections which are resistant to pentamidine.[1] In some regions, suramin has been used with pentamidine for *T. b. gambiense* infections but it has not been shown to be clinically superior to pentamidine alone.[2] Case reports have suggested that suramin with metronidazole[3] or eflornithine[4] could be useful in *T. b. rhodesiense* infections, although response to suramin plus eflornithine was disappointing in a study involving 6 patients.[5]
1. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/04/09)
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; **90**: 183–6.
3. Foulkes JR. Metronidazole and suramin combination in the treatment of arsenical refractory rhodesian sleeping sickness—a case study. *Trans R Soc Trop Med Hyg* 1996; **90**: 422.
4. Taelman H, *et al.* Combination treatment with suramin and eflornithine in late stage rhodesian trypanosomiasis: case report. *Trans R Soc Trop Med Hyg* 1996; **90**: 572–3.
5. Clerinx J, *et al.* Treatment of late stage rhodesiense trypanosomiasis using suramin and eflornithine: report of six cases. *Trans R Soc Trop Med Hyg* 1998; **92**: 449–50.

Adverse Effects

An immediate and potentially fatal reaction, with nausea, vomiting, shock, seizures, and loss of consciousness, may occur during the first injection of suramin sodium in some patients and thus it is usual practice to give a small test dose before starting treatment; toxicity is more likely in malnourished patients.

Abdominal pain, mouth ulceration, and skin reactions such as urticaria and pruritus may occur.

Other adverse effects include paraesthesia and hyperaesthesia of the palms and soles, skin eruptions, blood dyscrasias, fever, polyuria, increased thirst, raised liver enzyme values, fatigue, and effects on the eye including photophobia and lachrymation. Proteinuria is common; haematuria and casts in the urine may also occur. There have been occasional reports of adrenal insufficiency.

Effects on the blood. Thrombocytopenia has been reported in patients receiving suramin, generally during treatment for AIDS or cancer.[1-5] An immune-mediated mechanism has been proposed[3] although there is evidence that multiple mechanisms may be involved.[4] Other adverse effects on the blood include leucopenia or neutropenia,[1,5,6] anaemia,[1] deterioration of pre-existing lymphocytopenia,[6] and fatal myelosuppression.[6] Agranulocytosis and haemolytic anaemia have occurred rarely.
1. Levine AM, *et al.* Suramin antiviral therapy in the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; **105**: 32–7.
2. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41**: 299–307.
3. Seidman AD, *et al.* Immune-mediated thrombocytopenia secondary to suramin. *Cancer* 1993; **71**: 851–4.
4. Tisdale JF, *et al.* Severe thrombocytopenia in patients treated with suramin: evidence for an immune mechanism in one. *Am J Hematol* 1996; **51**: 152–7.
5. García-Schürmann JM, *et al.* Suramin treatment in hormone- and chemotherapy-refractory prostate cancer. *Urology* 1999; **53**: 535–41.
6. Rosen PJ, *et al.* Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. *J Clin Oncol* 1996; **14**: 1626–36.

Effects on the eyes. Late effects on the eyes associated with suramin include photophobia, lachrymation, and palpebral oedema. Keratopathy characterised by corneal deposits has been reported in patients receiving suramin. In a study of 114 patients receiving suramin for prostatic cancer, 13 developed corneal deposits similar to those reported with chloroquine therapy after 34 to 98 days of therapy.[1] Symptoms in 10 of the 13 included lachrymation and foreign body sensation. The remaining 3 patients were asymptomatic. Shifts in refractive error were also found. Keratopathy has also been reported in patients with AIDS receiving suramin.[2] In patients treated with suramin for ocular onchocerciasis, the incidence of optic atrophy was higher after 3 years than in untreated patients.[3] A prolonged inflammatory response to dying microfilariae in the optic nerve might be responsible, although a direct toxic or allergic effect could not be ruled out.
1. Hemady RK, *et al.* Ocular symptoms and signs associated with suramin sodium treatment for metastatic cancer of the prostate. *Am J Ophthalmol* 1996; **121**: 291–6.
2. Teich SA, *et al.* Toxic keratopathy associated with suramin therapy. *N Engl J Med* 1986; **314**: 1455–6.
3. Thylefors B, Rolland A. The risk of optic atrophy following suramin treatment of ocular onchocerciasis. *Bull WHO* 1979; **57**: 479–80.

Effects on the kidneys. In addition to the proteinuria commonly seen during suramin therapy, there have been reports of individual cases of renal glycosuria[1] and of acute renal failure.[2,3]
1. Awadzi K, *et al.* The chemotherapy of onchocerciasis XVIII: aspects of treatment with suramin. *Trop Med Parasitol* 1995; **46**: 19–26.
2. Figg WD, *et al.* Acute renal toxicity associated with suramin in the treatment of prostate cancer. *Cancer* 1994; **74**: 1612–14.
3. Smith A, *et al.* Acute renal failure in a patient receiving treatment with suramin. *Am J Clin Oncol* 1997; **20**: 433–4.

Effects on the nervous system. Neurological disorders reported in patients receiving parenteral suramin for the treatment of malignancies include a mild, distal axonal neuropathy and a more severe, inflammatory demyelinating neuropathy that is partially reversible and may resemble Guillain-Barré syndrome.[1] Severe polyneuropathy with generalised flaccid paralysis is dose dependent and has generally been associated with serum-suramin concentrations greater than 350 micrograms/mL,[2,3] but motor neuropathy was reported in 8 patients with serum concentrations of 275 micrograms/mL.[4]
1. Chaudhry V, *et al.* A prospective study of suramin-induced peripheral neuropathy. *Brain* 1996; **119**: 2039–52.
2. La Rocca RV, *et al.* Suramin-induced polyneuropathy. *Neurology* 1990; **40**: 954–60.
3. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41**: 299–307.
4. Bitton RJ, *et al.* Pharmacologic variables associated with the development of neurologic toxicity in patients treated with suramin. *J Clin Oncol* 1995; **13**: 2223–9.

Effects on the skin. Pruritus and urticaria may occur as hypersensitivity reactions to suramin. A prospective study[1] in 60 patients given high doses of intravenous suramin for the treatment of malignancies reported skin reactions, most commonly morbilliform reactions, in 82% of patients. Other reported skin effects were keratotic papules, UV recall, and urticaria. Most reactions occurred within the first 24 hours of therapy and resolved despite continued treatment. Late skin reactions include erythematous maculopapular rashes.[2] Severe reactions including erythema multiforme,[3] exfoliative dermatitis, and fatal toxic epidermal necrolysis[4,5] have been reported.
1. Lowitt MH, *et al.* Cutaneous eruptions from suramin: a clinical and histopathologic study of 60 patients. *Arch Dermatol* 1995; **131**: 1147–53.
2. O'Donnell BP, *et al.* Suramin-induced skin reactions. *Arch Dermatol* 1992; **128**: 75–9.
3. Katz SK, *et al.* Erythema multiforme induced by suramin. *J Am Acad Dermatol* 1995; **32**: 292–3.
4. May E, Allolio B. Fatal toxic epidermal necrolysis during suramin therapy. *Eur J Cancer* 1991; **27**: 1338.
5. Falkson G, Rapoport BL. Lethal toxic epidermal necrolysis during suramin treatment. *Eur J Cancer* 1992; **28A**: 1294.

Precautions

Suramin sodium should be used under close supervision, and the general condition of patients improved as far as possible before treatment starts. Patients who have a severe reaction to the first dose should never receive suramin again. It should not be used in elderly or infirm patients or in the presence of severe hepatic or renal disease. The urine should be tested before treatment starts and weekly during treatment; dosage should be reduced if moderate proteinuria develops and stopped if it becomes severe or if casts appear in the urine.

Pregnancy. Suramin has been reported to be teratogenic in *mice* but not in *rats*.[1] WHO[2] recommends that women necessary suramin should be used in pregnant women with *T. b. rhodesiense* trypanosomiasis, even those with meningoencephalitic disease, because melarsoprol is contra-indicated; in onchocerciasis, suramin treatment should be delayed until after delivery.
1. Mercier-Parot L, Tuchmann-Duplessis H. Action abortive et tératogène d'un trypanocide, la suramine. *C R Soc Biol* 1973; **167**: 1518–22.
2. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 07/04/09)

Pharmacokinetics

After intravenous injection, suramin becomes bound to plasma proteins and plasma concentrations over 100 micrograms/mL are maintained for several weeks. Unbound suramin is excreted in the urine; small amounts are excreted in the faeces. Suramin is widely distributed; concentrations in the kidney and adrenal glands are higher than those in other tissues. Penetration of suramin into the CSF appears to be poor.

The clinical pharmacokinetics of suramin were studied in 4 patients with AIDS given 6.2 g intravenously over 5 weeks.[1] Suramin accumulated during treatment and plasma concentrations exceeded 100 micrograms/mL for several weeks. After the last dose the terminal half-life of suramin ranged from 44 to 54 days. At least 99.7% was bound to plasma proteins. Renal clearance accounted for most of the elimination of suramin from the body. There appeared to be little or no metabolism of suramin.

In another study,[2] ten male patients with onchocerciasis received weekly infusions of suramin for 6 weeks, according to the dose regimen recommended by WHO (see p. 948.1). In these patients the median elimination half-life was about 92 days, and in each case, the peak plasma concentration remained below 300 micrograms/mL.

1. Collins JM, *et al.* Clinical pharmacokinetics of suramin in patients with HTLV-III/LAV infection. *J Clin Pharmacol* 1986; **26**: 22–6.
2. Chijioke CP, *et al.* Clinical pharmacokinetics of suramin in patients with onchocerciasis. *Eur J Clin Pharmacol* 1998; **54**: 249–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Germanin.

Teclozan *(USAN, rINN)*

NSC-107433; Téclozan; Teclozán; Teclozanum; Win-13146; Теклозан.

NN'-p-Phenylenedimethylenebis[2,2-dichloro-*N*-(2-ethoxyethyl)acetamide].

$C_{20}H_{28}Cl_4N_2O_4$=502.3

CAS — 5560-78-1.

ATC — P01AC04.

UNII — K9RIF0COUB.

Profile

Teclozan, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p. 931.2). It has been given orally in the treatment of intestinal amoebiasis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Falmonox; *Venez.*: Falmonox.

Tenonitrozole *(rINN)*

TC-109; Tenonitrozol; Ténonitrozole; Tenonitrozolo; Tenonitrozolum; Thenitrazole; Тенонитрозол.

N-(5-Nitrothiazol-2-yl)thiophene-2-carboxamide.

$C_8H_5N_3O_3S_2$=255.3

CAS — 3810-35-3.

ATC — P01AX08.

UNII — PBQ7WLE1WP.

Profile

Tenonitrozole is an antiprotozoal given in the treatment of trichomoniasis (p. 925.1). It is given orally in a dose of 250 mg twice daily with meals, for 4 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Atrican; *Rus.*: Atrican (Атрикан); *Ukr.*: Atrican (Атрикан).

Ternidazole *(rINN)*

Ternidazol; Ternidazolum; Тернидазол.

2-Methyl-5-nitroimidazole-1-propanol.

$C_7H_{11}N_3O_3$=185.2

CAS — 1077-93-6.

UNII — 4N8R018Q80.

Profile

Ternidazole is a 5-nitroimidazole antiprotozoal with properties similar to those of metronidazole (p. 936.1). It is an ingredient of preparations used for the treatment of vaginitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Tergynan (Тержинан); *Ukr.*: Tergynan (Тержинан).

Tilbroquinol *(pINN)*

Tilbroquinolum; Тильброхинол.

7-Bromo-5-methylquinolin-8-ol.

$C_{10}H_8BrNO$=238.1

CAS — 7175-09-9.

ATC — P01AA05.

UNII — P6SB125NHA.

Profile

Tilbroquinol is a halogenated hydroxyquinoline antiprotozoal with properties similar to those of diiodohydroxyquinoline (p. 931.1). It has been used with tiliquinol (below) in the treatment of intestinal infections including amoebiasis but less toxic drugs are preferred.

Adverse effects. A report of neurotoxicity, considered to be subacute myelo-opticoneuropathy, in a patient who had taken tilbroquinol with tiliquinol for 4 years.[1] Hepatotoxicity has also been reported[2] with this combination.

1. Sotter M, *et al.* Oxyquinoline toxicity. *Lancet* 1983; **i**: 709.
2. Caroli-Bosc F-X, *et al.* Hépatite aiguë due à l'association de tiliquinol et tilbroquinol (Intétrix). *Gastroenterol Clin Biol* 1996; **20**: 605–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Intetrix; *Rus.*: Intetrix (Интетрикс); *Ukr.*: Intetrix (Интетрикс).

Tiliquinol *(rINN)*

Tiliquinolum; Тилихинол.

5-Methylquinolin-8-ol.

$C_{10}H_9NO$=159.2

CAS — 5541-67-3.

UNII — 813OG1OGVG.

Profile

Tiliquinol has been used with tilbroquinol (above) in the treatment of intestinal infections including amoebiasis but less toxic drugs are preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Intetrix; *Rus.*: Intetrix (Интетрикс); *Ukr.*: Intetrix (Интетрикс).

Tinidazole *(BAN, USAN, rINN)*

CP-12574; Tinidatsoli; Tinidazol; Tinidazolas; Tinidazolo; Tinidazolum; Tynidazol; Тинидазол.

1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole.

$C_8H_{13}N_3O_4S$=247.3

CAS — 19387-91-8.

ATC — J01XD02; P01AB02.

ATC Vet — QJ01XD02; QP51AA02.

UNII — 033KF7V46H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tinidazole). An almost white or pale yellow, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Tinidazole). An almost white or pale yellow crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Tinidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p. 936.2) in the treatment of susceptible protozoal infections such as amoebiasis (p. 919.1), giardiasis (p. 921.3), and trichomoniasis (p. 925.1), and bacterial vaginosis (p. 174.1), and in the treatment and prophylaxis of anaerobic bacterial infections (p. 173.1). It has also been used in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease (p. 1816.2).

Tinidazole is usually given as a single daily oral dose with or after food; it is also given by intravenous infusion and as vaginal pessaries.

In symptomatic (invasive) **amoebiasis**, tinidazole treatment is usually followed with a luminal amoebicide. In intestinal amoebiasis, a single daily dose of 2 g is given orally for 2 or 3 days; in hepatic amoebiasis, 1.5 to 2 g as a single daily dose may be given for 3 days or occasionally up to 6 days.

A single dose of tinidazole 2 g is given orally in the treatment of **giardiasis**, **trichomoniasis**, and acute necrotising **ulcerative gingivitis**. In trichomoniasis, sexual partners should also be treated.

For details of doses in children, see below.

In **bacterial vaginosis**, a single 2-g dose of tinidazole is usually given orally, although higher cure rates have been achieved with a 2-g dose on 2 successive days or 1 g daily for 5 days.

For the treatment of most **anaerobic bacterial infections**, tinidazole is given orally, usually for 5 or 6 days, in an initial dose of 2 g followed on subsequent days by 1 g daily or 500 mg twice daily. If oral therapy is not possible, tinidazole may be given intravenously, 800 mg being infused as 400 mL of a 2 mg/mL solution at a rate of 10 mL/minute; this initial dose is followed by 800 mg daily or 400 mg twice daily until oral therapy can be substituted. For the *prevention* of postoperative anaerobic bacterial infections, 2 g is given orally about 12 hours before surgery. Alternatively 1.6 g is given as a single intravenous infusion before surgery.

For the treatment of **peptic ulcer disease**, tinidazole 500 mg twice daily has been given with clarithromycin and omeprazole for 7 days. Due to problems with resistance to tinidazole and macrolides a sequential regimen of a proton pump inhibitor with amoxicillin for 5 days, followed by the proton pump inhibitor with tinidazole (500 mg twice daily) and clarithromycin for a further 5 days has also been recommended.

Reviews.

1. Manes G, Balzano A. Tinidazole: from protozoa to Helicobacter pylori—the past, present and future of a nitroimidazole with peculiarities. *Expert Rev Anti Infect Ther* 2004; **2**: 695–705.
2. Fung HB, Doan TL. Tinidazole: a nitroimidazole antiprotozoal agent. *Clin Ther* 2005; **27**: 1859–84.
3. Nailor MD, Sobel JD. Tinidazole for bacterial vaginosis. *Expert Rev Anti Infect Ther* 2007; **5**: 343–8.
4. Granizo JJ, *et al.* Tinidazol: un anaerobicida clásico con múltiples usos potenciales en la actualidad. *Rev Esp Quimioter* 2009; **22**: 106–14.
5. Dickey LJ, *et al.* Guidelines for the treatment of bacterial vaginosis: focus on tinidazole. *Ther Clin Risk Manag* 2009; **5**: 485–9.
6. Armstrong NR, Wilson JD. Tinidazole in the treatment of bacterial vaginosis. *Int J Womens Health* 2010; **1**: 59–65.

Administration in children. Tinidazole may be given to children for the treatment of susceptible protozoal infections. For intestinal or hepatic **amoebiasis** an oral dose of 50 to 60 mg/kg daily (to a maximum of 2 g) is given. Intestinal amoebiasis is treated for 3 days and hepatic amoebiasis for 5 days. Treatment of symptomatic (invasive) amoebiasis must be followed by a luminal amoebicide to eradicate any surviving organisms from the lumen of the large intestine.

In the treatment of **giardiasis** or **trichomoniasis** 50 to 75 mg/kg (to a maximum of 2 g) as a single oral dose is given; it may sometimes be necessary to repeat this dose once.

Administration in renal impairment. The elimination of tinidazole is largely unchanged in patients with impaired renal function (see under Pharmacokinetics, p. 950.1) and dosage adjustment is not generally considered necessary. However tinidazole is removed by haemodialysis, and patients may need additional doses to compensate; a dose equivalent to 50% of the recommended dose may be given at the end of haemodialysis.

Adverse Effects and Precautions

As for Metronidazole, p. 937.3.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that the use of tinidazole by mothers during breast feeding may be of concern, since it is mutagenic *in vitro*. After single-dose therapy, breast feeding may be stopped for 12 to 24 hours to allow excretion of the dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/06/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tinidazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Shock. An acute severe toxic reaction, considered not to be allergic, occurred in a healthy subject shortly after the intravenous infusion of tinidazole 1.6 g over 80 minutes.[1] He fainted for about 10 seconds and low blood pressure, nausea, and tiredness persisted for several hours. He had spasms in the left arm but no generalised convulsions. Anaphylactic shock has also been reported,[2] with severe

bronchospasm and subsequent development of Stevens-Johnson syndrome, in a patient who had reactions of increasing severity after 3 separate exposures to oral tinidazole.

1. Aase S, *et al.* Severe toxic reaction to tinidazole. *Eur J Clin Pharmacol* 1983; 24: 425–7.
2. Singhal SS, Rataboli PV. Anaphylaxis and hypersensitivity syndrome reactions in increasing severity following repeated exposure to tinidazole. *J Postgrad Med* 2005; 51: 243–4.

Interactions

Although licensed product information suggests that tinidazole may, like metronidazole (p. 939.2), produce a disulfiram-like reaction with alcohol there do not appear to be any published reports to support this.

Pharmacokinetics

The pharmacokinetics of tinidazole resemble those of metronidazole although the half-life is longer.

Tinidazole is rapidly and almost completely absorbed after oral doses and, typically, a peak plasma concentration of about 40 micrograms/mL occurs 2 hours after a single 2-g dose, falling to about 10 micrograms/mL at 24 hours and 2.5 micrograms/mL at 48 hours; concentrations above 8 micrograms/mL are maintained by daily maintenance doses of 1 g. Comparable concentrations occur with equivalent intravenous doses. The plasma elimination half-life of tinidazole is 12 to 14 hours.

Tinidazole is widely distributed and concentrations similar to those in plasma have been achieved in bile, breast milk, CSF, saliva, and a variety of body tissues; it also crosses the placenta and blood-brain barrier. Only 12% is reported to be bound to plasma proteins. An active hydroxy metabolite has been identified.

Unchanged drug and metabolites are excreted in the urine and, to a lesser extent, in the faeces.

References.

1. Wood BA, *et al.* The pharmacokinetics, metabolism and tissue distribution of tinidazole. *J Antimicrob Chemother* 1982; 10 (suppl A): 43–57.
2. Karhunen M. Placental transfer of metronidazole and tinidazole in early human pregnancy after a single infusion. *Br J Clin Pharmacol* 1984; 18: 254–7.
3. Evaldson GR, *et al.* Tinidazole milk excretion and pharmacokinetics in lactating women. *Br J Clin Pharmacol* 1985; 19: 503–7.
4. Wood SG, *et al.* Pharmacokinetics and metabolism of ^{14}C-tinidazole in humans. *J Antimicrob Chemother* 1986; 17: 801–9.

Renal impairment. Single-dose studies indicate that the pharmacokinetics of tinidazole in patients with chronic renal failure are not significantly different from those in healthy subjects and that no modification of tinidazole dosage is necessary. However, tinidazole is rapidly removed by haemodialysis.[1,2]

1. Flouvat BL, *et al.* Pharmacokinetics of tinidazole in chronic renal failure and in patients on haemodialysis. *Br J Clin Pharmacol* 1983; 15: 735–41.
2. Robson RA, *et al.* Tinidazole pharmacokinetics in severe renal failure. *Clin Pharmacokinet* 1984; 9: 88–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fasigyn; Gynormal; Ladylen Duo; *Austral.*: Fasigyn; Simplotan; *Belg.*: Fasigyn; *Braz.*: Amplium; Facyl; Fasigyn; Ginosutin†; Pletil; Tinoral; *Chile*: Fasigyn; Troxxil; *China*: Bi Shi (比适); Dabao (达保); Dikexin (迪克新); Fu Lu Ning (福路宁); Hua Er Pu (华尔复); Ji De (济得); Jie Luo Lin (捷洛林); JieLi (捷力); JinHe (津和); Kai Fu Xin (凯服新); Ke Li Tai (可立泰); Le Jing Yi (乐净怡); Login (乐净); Pu Luo Shi (普洛施); Shuanghedida (双鹤获达); Tinijing (替尼津); Xi Pu Ning (希普宁); Xiaoli (晓力); Yi Qi (益祺); Yu Ning (裕宁); *Fr.*: Fasigyne; *Gr.*: Fasigyn; Trichogin; *Hong Kong*: Fasigyn; *India*: Amebamagma; Costini; Cozit; Datisole; Enidazol; Fasigyn; Norigyl; Tiniba; Tinidafyl; Tinifas; Tinvista; *Indon.*: Fasigyn†; Flatin†; *Israel*: Fasigyn†; Protocide; *Ital.*: Trimonase; *Malaysia*: Tindol; *Mex.*: Amebysol†; Ametricid; Estovyn-T; Fasigyn; Induken; Trinigyn; Triseptil; *NZ*: Dyzole; *Port.*: Fasigyn; *Rus.*: Fasigyn (Фазижин); Tiniba (Тиниба); *S.Afr.*: Fasigyn; *Singapore*: Fasigyn; *Spain*: Tricolam; *Swed.*: Fasigyn; *Switz.*: Fasigyne†; *Thai.*: Asiazole-TN; Fasigyn; Funida; Gynogena; Idazole; Leuco; Pagyn; Sporinex†; Tinazole; Tivagil; TM Dazole; Tonid†; Trichonas; Tricogyn; Tricozone; *Turk.*: Fasigyn; *UK*: Fasigyn; *USA*: Tindamax; *Venez.*: Fasigyn; Pangamil.

Multi-ingredient Preparations. *Arg.*: Aduar; Fasigyn Nistatina; Gynormal; Helmint Compuesto; Ladylen; Mebutar Compuesto; Nistinol†; Tru Compuesto; *Braz.*: Amplium-G; Anfugine; Cartrax; Colpolase†; Duozol; Facyl M; Ginec; Gino-Colon; Gino-Pletil; Ginosutin-M†; Gynben; Gynomax; Gynopac; Poliginax; Seczol; Takil; Tinin; Tiotrax; Travogyn; Trinizol M; Vulnagen; *Chile*: Doxifen; Exomicol; Famidal; Ginecopast Dual; Ginecopast; Ginedazol Dual; Ginedazol; Medidos; Mizonase; Tinidazol Compuesto; *China*: Weisanlian (胃三联); *India*: Actiflox-T; Actinor-TZ; Adcip-TZ; AFlox-TZ; Alcip-TZ; Alcipro-TN; Alof-T; Alvi; Amebis Forte; Amibex-TZ; Amicline Plus; Antibic-DF; Aricip-TZ; Atocip-TZ; Aviflox-TZ; Avilox-TZ; Azostat; Bacter-TZ; Baycip-TZ; Biocip-TZ; Bioflox-TZ; C-Nor Plus; Cancap-Kit; Candizole-T†; Caniron-TZ; Casflox-TZ; Caspro-TZ; Chic-TZ; Cebect-TZ; Cebran-TN; Ceepro-TZ; Ceflox-TZ; Cefobac-TD; Cefobac-TDH; Ceplox-TZ; Cezel-PT; Cidalox-TZ; Ciflon-TZ; Cifomed-TZ; Cifran-CT-H; Cifran-CT; Cina-TZ; Cinant-TZ; Cinodin-TZ; Cinzole; Cip-TZ; Cipcin-TNZ; Cipcot-TZ; Cipflox-TZ; Cipgen TZ; Cipglow-TZ; Ciplox TZ; Cipro-TZ; Ciprobid-TZ; Ciprobiotic-TN; Ciprodac-TZ; Ciprodex-TZ; Ciprogyl; Ciprolar-T; Ciprolet-A; Ciprolet-AH; Cipronat-TZ; Cipronij-TZ; Ciropet-TZ; Ciprosym-TZ; Ciprotini; Ciprotiz; Ciprotum-TZ; Ciprova-T; Ciprovec-TZ; Ciprowin-TZ; Ciprozee-TZ; Ciptam-CT; Ciptech-CT; Cipti; Ciptini; Cipure-TZ; Cipven-TZ; Cipwin-TZ; Cipzy-TZ; Ciral-TZ; Citi; Citibid; Citizol; Ciwi-TZ; Clodaz-V6; Clofcin-T; Conaz; Cozan-T; CPF-TZ; CT-Robes; Cucin-T; Cymex-TZ; Cyprin-TD; Dandrid; Dazonor; Depci-TZ; Diaba; Dialox; Diarlop-CT; DLotin MPS; Doact-TZ; Donnagyl-H; Dox-M TZ; Doxylin-TZ; DTO; Duonor; Dysnilox; E-Cip-TZ; Eldazole; Elnor-TZ; Elquin-TZ; Emdox-TZ; Emflox-TZ; Emucin-TN; Entamizole TN; Enteroflox-T; Entrolate; Eufox-TZ; Falcon-TZ; Festive-TZ; Flobacin-TZ; Flocin-TZ; Flocipron-T; Flocy TZ; Flontin; Florida-T; Floxur-TZ; Flucos-TZ; Flucoti; Flutini Kit; Fluzon-T; Forcan TZ; Formax; Ftz; Fusys-TZ; Gastrogyl Plus; Gastrogyl; Genflox TZ; Ginal-V; Ginal-V; Ginlac-V; Glocip-TZ; Gramoneg-TN; Harflox-T; Harpoon-DD; Harpoon-TZ; Helibact; Heligo; Helikit; Helipac; Hicip-TZ; Hill-V; HP Kit; Idometrin-D; Inflobid TZ; Jox-TZ; K-Cip-TZ; Kurecip-TZ; L-Cot; Labocip-TZ; Lansi Kit; Lexflox-TZ; Lexof-TZ; Locip-TZ; Lokit-Kit; Lomet-CT; Loxitin-P; Loxitin; Loxone-T; LTC-Kit; Lucipro-T; Mapci-TZ; Mapgyl; Matrix; Megaflox-TZ; Meganeg; Microcip-TZ; Microflox-CT; Mini-Citizol; Mintocip-TZ; Mofcare-TZ; N-Flox TZ; N-Tiz; Nedge; Neflox-TZ; Nexcip-TZ; Nitdin-TZ; Nor T; Nor-T; Noragyl; Norazol; Norbactin-Z; Nordys; Norfen TZ; Norflox TZ; Norilet-A; Norin-TD; Norlex-TZ; Norlon; Normax TZ; Normide-CZ; Normide; Normij-TZ; Nort; Norzee-TZ; Notisym-LB; Nox-TZ; NT-Z; NTD; Nucip-TZ; Nuforce Kit; Obactin-TZ; Obit-TZ; Ofac-T; Ofacin-TZ; Ofal-TZ; Ofax-TZ; Ofcit-T; Ofla-TZ; Oflabin-TZ; Oflamed-TZ; Oflavid-TZ; Oflawin-TZ; Ofler-TZ; Oflin-TZ; Oflo-TZ; Oflocos-TZ; Ofloden-T; Oflomac-TZ; Oflon-TZ; Ofloren-TZ; Oflostar-TZ; Oflox TZ; Ofloxin-TZ; Ofo-TZ; Ofpil-TZ; Ofral-TZ; Ofspan-TZ; Oft; Oftini; Ofrum-TZ; Ofven-TZ; Ojen-TZ; Okaflox-TZ; Olfi TZ; Olife-TZ; Oltaur-TZ H; Omepraz-HP Kit; Omibact-TZ; Omniflox-CT; Omoxitin; Oniflox; Orpic-T; Osani-T; Osiflox-TZ; OTC HP Kit; Oxiflox TZ; Oxo-TZ; Oxwal-TZ; Panzer-TZ; Parabact†; Pylokit; Tinidafyl Plus; Tinvista-CP; Tinvista-NF; Wotinex; *Indon.*: Fasigyn-Nystatin†; *Ital.*: Fasigin N; *Malaysia*: Pylobact Combi; *Mex.*: Afumix; Pasigyn VT; Mebeciclol; *Rus.*: Ciprolet A (Ципролет А); Pylobact (Пилобакт); *Turk.*: Gynomax; *Ukr.*: Cifran CT (Цифран CT).

Toltrazuril *(BAN, USAN, rINN)*

Bay-Vi-9142; Toltrazurilo; Toltrazurilum; Тольтразурил.

1-Methyl-3-(4-[*p*-[(trifluoromethyl)thio]phenoxy]-*m*-tolyl)-s-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.

$C_{18}H_{14}F_3N_3O_4S$=425.4

CAS — 69004-03-1.

ATC Vet — QP51AJ01.

UNII — QVZ3IAR3JS.

Profile

Toltrazuril is an antiprotozoal used in veterinary practice for the treatment of coccidiosis in poultry and calves, and to treat coccidian infections, including isosporiasis, in piglets.

Tryparsamide *(rINN)*

Glyphenarsine; Triparsamida; Tryparsam.; Tryparsamidum; Tryparsone; Трипарсамид.

Sodium hydrogen 4-(carbamoylmethylamino)phenylarsonate hemihydrate.

$C_8H_{10}AsN_2NaO_4.½H_2O$=305.1

CAS — 554-72-3 (anhydrous tryparsamide); 6159-29-1 (tryparsamide hemihydrate).

UNII — 4NN21HAX16.

Profile

Tryparsamide, a pentavalent arsenical compound, is a trypanocide which penetrates into the CSF and has been used with suramin in the treatment of late-stage African trypanosomiasis due to *Trypanosoma brucei gambiense*, as an alternative to melarsoprol or eflornithine (see p. 925.2). However, because of its toxicity, especially the risk of blindness resulting from damage to the optic nerve, other drugs are preferred.

For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p. 2448.3. Like melarsoprol, tryparsamide can cause encephalopathy.

Antivirals

The drugs described in this chapter are used in the treatment of viral infections; they may also be used to provide protection, usually for a brief period only, against infection. For most viral infections drug treatment has to be started early in the infection to be effective and inhibit the replicating virus. There is little evidence that antiviral drugs affect latent or nonreplicating viruses. They do not provide an alternative to available immunisation for the long-term prophylaxis of viral infection—for details of such treatment see the chapter on Vaccines Immunoglobulins and Antisera, p. 2373.1.

Choice of Antiviral

Antiviral drugs are effective for the treatment and prophylaxis of a range of viral infections as described below. Non-specific symptomatic and supportive treatments are also important in the management of viral infections. Those viral infections not amenable to antiviral drug therapy include mumps, poliomyelitis, rabies, and rubella.

Common cold

The common cold is a term used for viral upper respiratory tract illness. Rhinoviruses are the commonest cause in all age groups. Adenoviruses, coronaviruses, enteroviruses, and metapneumovirus may also be responsible. Infecting organisms in these groups may be of many different serotypes.

Colds are usually self-limiting and last for 4 to 10 days. Symptoms include nasal discharge and stuffiness, sneezing, sore throat, and cough (see also p. 1651.2); there is little or no malaise, headache, or fever. Colds may predispose to concurrent or subsequent bacterial infection of the upper respiratory tract; exacerbation of asthma or chronic obstructive pulmonary disease may also occur. Acute otitis media or acute sinusitis may result from obstruction of the Eustachian tube and mucosal swelling.

The successful development of a single cure or vaccine is unlikely, given the variety of causative viruses and large number of serotypes. Treatment is symptomatic. Analgesics, cough suppressants, antihistamines, and decongestants relieve symptoms but do not tend to reduce the duration of illness. Antibacterial and antiviral therapy has consistently failed to show any benefit and antibacterials are indicated only if there is secondary bacterial infection.[1] Very large doses of vitamin C have been widely used to prevent and treat colds but a systematic review[2] has concluded that, despite some evidence of benefit in published studies, its failure to reduce the incidence of colds in the normal population indicated that routine high-dose prophylaxis was not justified for community use; it might, however, be of use in persons exposed to brief periods of severe physical exercise or to cold environments. For treatment, no benefit has been found for doses up to 4 g, although one study reported equivocal benefit from a dose of 8 g given at the onset of symptoms.[2] Other drugs[3] tried have included mast-cell stabilisers, interferon alfa-2b, and zinc salts. Intranasal interferons have shown some benefit in prophylactic use, but high incidences of unacceptable nasal adverse effects have resulted in interferons failing to fulfill their early promise. Results of studies of oral or intranasal zinc treatment have been variable, although a systematic review concluded that oral zinc reduced the duration and severity of common cold symptoms when used therapeutically, and that it reduced the incidence of the common cold in healthy children when used prophylactically.[4] There is little consistent evidence to support the use of *Echinacea* for treatment or prevention of colds.[5,6] However, available *Echinacea* products differ greatly and there is some evidence that treatment with those based on the aerial parts of *E. purpurea* might be effective in adults if started early.[5] Pleconaril, a viral capsid binder, has also been studied but there have been concerns with the oral formulation over viral resistance and interactions with oral contraceptives; the intranasal formulation appears more promising.[7]

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Encephalitis

Encephalitis refers to an acute inflammatory process affecting the brain parenchyma; it is distinct from meningitis which is an inflammation of the meninges. Meningoencephalitis involves both the brain parenchyma and meninges. Viral infection is the commonest cause of encephalitis,[1-3] with the herpes simplex virus (p. 955.2) being the commonest organism involved in immunocompetent individuals. Other viruses that may cause encephalitis include enteroviruses (e.g. poliovirus), Epstein-Barr, influenza, Lassa fever, measles and mumps (paramyxoviruses), rabies, rubella, and varicella zoster. CMV and HIV cause encephalitis almost exclusively in immunocompromised individuals. In the 1990s, Hendra virus and Nipah virus, which belong to the paramyxoviridae family, were newly discovered causes of encephalitis. The reservoir for these viruses is *bats*, but transmission to humans can occur via close contact with secondary hosts such as *horses* and *pigs*. A group of viruses known as the arthropod-borne encephalitis viruses (arboviruses) may cause infections in which encephalitis is a major clinical feature. They include:

- bunyaviruses including California encephalitis virus and La Crosse virus (both transmitted by mosquitoes)
- flaviviruses (previously arbovirus Group B) including Japanese encephalitis virus, St Louis encephalitis virus, Murray Valley encephalitis virus, Rocio virus, and West Nile virus (all transmitted by mosquitoes) and the tick-borne viruses of this group, louping ill virus, Powassan virus, and the Eastern and Western subtype viruses
- reoviruses including Colorado tick fever virus (transmitted by ticks)
- togaviruses including Eastern, Western, and Venezuelan equine viruses (transmitted by mosquitoes)

In endemic regions viral encephalitis should be suspected in patients presenting with fever, headache, neck rigidity, altered level of consciousness (which may range from drowsiness to coma), and signs of diffuse cerebral dysfunction (hallucinations, psychosis, personality changes, and agitation). Seizures are common and patients who recover from encephalitis may be left with permanent neurological damage.

Since herpes simplex virus is the commonest cause of viral encephalitis, it is recommended that patients with encephalitis be given intravenous aciclovir empirically until the causative virus has been identified. (Antibacterial treatment for meningitis may also be given empirically until the cause of symptoms has been established; doxycycline should be used if rickettsial or ehrlichial infections are suspected.)[5] No specific treatment exists for non-herpetic encephalitis (although investigational treatments, including passive immunisation and the use of inhibitory RNA molecules, are under development[6]), and patients must be managed with vigorous supportive care. Corticosteroids are advocated in some circumstances,[4] but their use is controversial. Oseltamivir may be considered for infections caused by the influenza virus, ribavirin for infections with measles or Nipah virus, and interferon alfa-2 for infections caused by the St Louis encephalitis virus.[5] Pleconaril is under investigation for use in enteroviral encephalitis. Control of mosquito and tick populations in endemic areas and minimising contact with these vectors are important means of preventing infections. Japanese encephalitis vaccine and tick-borne encephalitis vaccine are available for active immunisation of individuals at risk of infection and tick-borne encephalitis immunoglobulins are available in some countries for passive immunisation against infection.

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4. Solomon T, *et al.* Viral encephalitis: a clinician's guide. *Pract Neurol* 2007; 7: 285–302.
5. Tunkel AR, *et al.* Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 47: 303–27.
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Gastro-enteritis

Gastro-enteritis (inflammation of the stomach and intestines) may be caused by viruses, bacteria, or protozoa.[1,2] Viral gastro-enteritis is an important cause of diarrhoea, especially in children and immunocompromised patients. Viruses causing diarrhoea and other gastrointestinal symptoms include calicivirus (such as norovirus and sapovirus), and rotavirus, as well as adenovirus and astrovirus.

- Rotavirus infection is recognised as a prominent cause of endemic acute diarrhoea in infants and young children and may occasionally cause acute or chronic diarrhoea in AIDS patients. Infection may be subclinical, although symptomatic rotavirus infection usually presents with fever and vomiting for 2 to 3 days, followed by watery diarrhoea that lasts for 4 to 5 days. Other symptoms include abdominal cramps and headache.
- Noroviruses (such as the Norwalk virus) are a more common cause of viral gastro-enteritis in older children and adults, but do not appear to cause severe disease in infants. They have been the cause of waterborne outbreaks of gastro-enteritis in nursing homes, military bases, and cruise ships.
- Sapoviruses (such as the Sapporo virus) are more commonly seen in young children. While illness resulting from these viruses is usually mild and lasts for 24 to 72 hours, the presenting symptoms are usually nausea and abdominal cramps. Other symptoms include diarrhoea, vomiting, headache, myalgias, and low-grade fever.
- CMV is an important cause of diarrhoea in AIDS (see HIV-associated Wasting, p. 959.1).

In acute diarrhoea of any cause it is most important to maintain hydration by preventing and replacing fluid and electrolyte loss, especially in infants and the elderly (see p. 1808.2). For further discussion see Oral Rehydration Solutions, p. 1782.1. Antivirals are not used in the management of viral diarrhoeas, except for that caused by CMV, where ganciclovir, valganciclovir, or foscarnet may be beneficial. A 3-day course of oral nitazoxanide was found to significantly reduce the duration of rotavirus disease in young children.[3] Frequent handwashing and good personal hygiene may prevent person-to-person spread of infection. Washing of contaminated clothing and surfaces, and boiling of contaminated water will also assist in preventing infection. Several live oral rotavirus vaccines (p. 2416.1) for use in the prevention of childhood diarrhoea have been developed and some are now licensed.

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2. Casburn-Jones AC, Farthing MJG. Management of infectious diarrhoea. *Gut* 2004; 53: 296–305.
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Haemorrhagic fevers

The viral haemorrhagic fevers are a group of viral illnesses characterised by a febrile illness that in some patients may be followed by severe bleeding, progressive organ failure, and death. The viruses are typically transmitted by mosquitoes, ticks, or rodents, and are largely geographically restricted. The more important viruses responsible for haemorrhagic fevers in man include:

- arenaviruses causing South American haemorrhagic fever syndromes (including Argentine, Bolivian, Brazilian, and Venezuelan haemorrhagic fever) and Lassa fever (transmitted by rodents)
- filoviruses causing Ebola and Marburg haemorrhagic fever, the natural host for which is unknown
- flaviviruses (previously arbovirus Group B) causing dengue fever and yellow fever (transmitted by mosquitoes), and Kyasanur forest fever and Omsk haemorrhagic fever (transmitted by ticks)
- hantaviruses causing haemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (transmitted by rodents)
- nairovirus causing Crimean Congo haemorrhagic fever (transmitted by ticks)
- phlebovirus causing Rift Valley fever (transmitted by mosquitoes)

Specific symptoms and the incubation time vary according to the infecting virus; in general the incubation time is short (up to 21 days but commonly less than 7 days) and followed by sudden (or, in the case of Lassa fever, more gradual) onset of fever, headache, myalgia, rash, and gastrointestinal disturbances such as abdominal pain, anorexia, diarrhoea, nausea, and vomiting. In patients who develop severe haemorrhagic manifestations (skin or mucosal bleeding, haematemesis, haematuria, or melaena), hepatitis, circulatory, renal, and respiratory failure, and coma are common. Depending on the causative virus, jaundice (yellow fever and Crimean Congo fever), muscle and joint pains (dengue fever), or pulmonary symptoms (hantavirus) may be more pronounced. Mortality is variable and ranges from less than 5% in dengue haemorrhagic fever and Lassa fever with optimal supportive care, to 15 to 30% in yellow fever and Crimean Congo haemorrhagic fever, and 70 to 80% in severe Ebola and Marburg virus infections.

Infection precautions, source isolation, and optimal supportive care are cornerstones of the management of viral haemorrhagic fevers. Vector control and prevention of bites are very important. There is generally no specific drug treatment for haemorrhagic fevers, although ribavirin may reduce mortality in patients with Lassa fever or haemorrhagic fever with renal syndrome, and possibly in Crimean Congo and Bolivian haemorrhagic fevers. Vaccines have been developed for the active immunisation of individuals at risk of Argentine haemorrhagic fever, Rift Valley fever, and yellow fever, and others are being developed for dengue fever and haemorrhagic fever with renal syndrome. Studies are ongoing for a vaccine against Ebola and Marburg viruses. Crimean Congo haemorrhagic fever immunoglobulins are available in some countries for passive immunisation against the disease. Guidelines for the prevention, control, and treatment of dengue and yellow fevers have been produced by WHO[1,2] and related organisations.[3] Guidelines for the management of haemorrhagic fevers have been published for some European countries.[4,5] The Pan American Health Organization[6] and the CDC[7] have also produced guidelines for the management of hantavirus pulmonary syndrome.

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Hepatitis

Though hepatitis may have many causes, viral hepatitis describes infections caused by viruses that mainly target the liver. Five hepatitis viruses are recognised to be primarily responsible for infection in humans and have been named hepatitis A, B, C, D, and E. Hepatitis may also occur as part of the clinical course of other viral infections, including CMV, Epstein-Barr virus, herpes simplex virus, rubella, varicella-zoster, and yellow fever infections.

Hepatitis A and E are spread via the faecal-oral route. Hepatitis B, C, and D are spread via contaminated blood and blood products, perinatal transmission, or sexual contact. All of these viruses may cause acute and occasionally fulminant hepatitis; hepatitis B, C, and D viruses can also cause chronic hepatitis. The herpesviruses may cause hepatitis during primary infection or during reactivation of a latent infection in immunocompromised persons. (For discussion on the management of herpesvirus infections, see p. 954.1.) Yellow fever virus is transmitted by mosquitoes and may cause fulminant hepatitis in non-immunised persons.

Acute viral hepatitis results in hepatocyte necrosis and inflammation of the liver. Clinical presentation ranges widely from asymptomatic infection to fulminant hepatic failure. Symptomatic acute hepatitis is characterised by abdominal pain, anorexia, fatigue, jaundice, low-grade fever, nausea, vomiting, and raised liver enzymes (AST and ALT). Chronic viral hepatitis is commonly asymptomatic but may result in hepatic fibrosis, cirrhosis, or hepatocellular carcinoma. Acute and chronic hepatitis may be complicated by fulminant hepatitis and liver failure, characterised by hepatic encephalopathy, coma, and death. As HIV and hepatitis B and C share risk factors for transmission, there are a significant number of people co-infected with 2 or all 3 viruses. HIV and hepatitis B or C co-infected patients have been found to have higher rates of hepatitis-related morbidity and mortality, with accelerated progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[1]

Viral hepatitis can be **prevented** by active immunisation against hepatitis A, hepatitis B, and yellow fever. Vaccination against hepatitis A is recommended, for example, for travellers to endemic regions, haemophiliacs, and for those considered to be at high risk due to their occupation or lifestyle (see p. 2388.3). Postexposure prophylaxis with hepatitis A immunoglobulin is recommended in some countries for household and intimate contacts of patients with hepatitis A infection, while others recommend normal immunoglobulins. Vaccination with hepatitis B vaccine is frequently recommended as part of the infant immunisation schedules and for non-immunised infants and adults at risk of infection (see, p. 2389.3). Hepatitis B immunoglobulin is recommended for passive immunisation of individuals exposed to a patient infected with the hepatitis B virus and after liver transplantation in persons infected with the hepatitis B virus, in order to prevent hepatitis B virus induced damage to the grafted liver (see, p. 2389.2). Yellow fever vaccination is recommended for persons at high risk of infection, including travellers to endemic areas and may be considered as part of the standard infant immunisation schedule in countries where the virus is endemic (see, p. 2424.3).

The **treatment of acute hepatitis** infections is largely symptomatic, as no effective antiviral therapy is available. Acute hepatitis B infection resolves without therapy in the majority of immunocompetent adults. A small pilot study[2] reported rapid clinical and biochemical responses to *lamivudine* in 13 of 15 patients with severe acute hepatitis B infection. Acute hepatitis C[3] is more commonly asymptomatic but, if diagnosed, therapy with an *interferon alfa* may be considered[4] as there is some evidence that they may reduce the risk of progression to chronic infection.[5] A study[6] in a small number of patients with acute hepatitis C concluded that if spontaneous clearance has not occurred by 12 weeks, a 6-month course of peginterferon alfa-2b should be given, as response rates to antiviral therapy are higher in patients with acute infection compared with those with established infection. The American Association for the Study of Liver Diseases (AASLD)[5] has stated that either interferon or peginterferon given for a period of 12 or 24 weeks may be considered for the treatment of acute hepatitis C if the infection persists 2 to 3 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[7] and by the Scottish Intercollegiate Guidelines Network.[8] The AASLD also states that no recommendation can be made for or against the addition of ribavirin and its use should be evaluated on a case-by-case basis.[5]

Treatment of chronic hepatitis B aims to achieve seroconversion from e antigen (HBeAg)-positive to e antigen-negative chronic infection (which is associated with lower rates of viral replication and lower rates of disease progression), to suppress viral replication, to delay the progression of chronic hepatitis to cirrhosis or hepatocellular carcinoma, and to treat extrahepatic complications such as glomerulonephritis. Complete suppression of viral replication is important to reduce the risk of viral resistance. Treatment is only recommended in patients with active or advanced liver disease and with high levels of HBV DNA. Drugs used for the treatment of chronic hepatitis B include immune modulators (interferon alfa-2b and peginterferon alfa-2a) and nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir).[9-11] Emtricitabine is being investigated for use in chronic hepatitis B[9,10] but studies with clevudine have been stopped due to serious toxicity.[12]

Interferon alfa was the first drug approved for the management of chronic hepatitis B. A meta-analysis[13] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HBeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels.[12] Studies have suggested that subcutaneous *peginterferon alfa* is as effective or slightly more effective than interferon alfa given subcutaneously.[12] Results from various studies[14] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[15] and HBeAg-negative patients with chronic hepatitis B,[16] when peginterferon alfa was given subcutaneously once weekly for 48 weeks.

Oral *lamivudine* has a similar efficacy to interferon but fewer adverse effects. Studies[17,18] have shown favourable effects on histologic, virologic, and biochemical features of the disease from long-term therapy, including decreased disease progression and progression to hepatocellular carcinoma in patients with cirrhosis or advanced fibrosis. In HBeAg-positive patients, treatment with lamivudine is generally continued for at least 6 months after seroconversion, while HBeAg-negative patients may need indefinite treatment due to high relapse rates when treatment is stopped.[12]

Studies with daily oral *adefovir dipivoxil* for 48 weeks have shown a mean drop in hepatitis B viral DNA of about 3.5 logs (factors of 10) in patients with HBeAg-positive chronic hepatitis B[19] and of about 4 logs in patients with HBeAg-negative chronic hepatitis B.[20] When adefovir dipivoxil was continued in HBeAg-negative patients for 144 weeks benefit was maintained whereas viral load rebounded in those patients who stopped treatment at 48 weeks.[20] Hepatitis B virus DNA was undetectable in 71% and 79% of patients after 96 and 144 weeks of treatment respectively.[20] Most HBeAg-positive and HBeAg-negative patients also had improvements in serum-ALT and liver histology.[19,20]

Other oral antiviral drugs approved for the treatment of chronic hepatitis B, including in patients with lamivudine-resistant disease, are entecavir and telbivudine. Studies with daily oral *entecavir* for 48 weeks have shown a mean drop in hepatitis B viral DNA of about 6.9 logs in patients with HBeAg-positive chronic hepatitis B[21] and of about 5 logs in patients with HBeAg-negative chronic hepatitis B.[22] Entecavir treatment continued through to 96 weeks, in those patients with HBeAg-positive hepatitis B, continued to show benefit.[23] In both these studies entecavir was found to be more potent than oral lamivudine in suppressing hepatitis B virus. *Telbivudine* was reported to be superior to lamivudine in patients with HBeAg-positive chronic hepatitis B and as effective as lamivudine in those with HBeAg-negative disease after 52 weeks of treatment;[24] after 104 weeks of treatment telbivudine was reported to be superior to lamivudine in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B.[25] A small open label study[26] with telbivudine or adefovir for 52 weeks, or adefovir for 24 weeks followed by telbivudine for 28 weeks, in patients with HBeAg-positive hepatitis B, reported greater and more consistent reductions in HBV DNA with telbivudine than with adefovir after 24 weeks of treatment. After 52 weeks, HBV DNA suppression was greater in patients given continuous telbivudine or who switched from adefovir to telbivudine after 24 weeks than in those given adefovir for 52 weeks. The most recent oral antiviral drug to be approved for the treatment of chronic hepatitis B is *tenofovir disoproxil fumarate*. Studies with daily oral tenofovir for 48 weeks reported superior antiviral efficacy compared with adefovir dipivoxil.[27] A systematic review and meta-analysis[28] compared the relative short-term (1-year) treatment efficacy of lamivudine, peginterferon alfa, adefovir, entecavir, telbivudine, and tenofovir in treatment-naive patients with chronic hepatitis B. Tenofovir was the most effective treatment in HBeAg-negative patients; in those who were HBeAg-positive, tenofovir and entecavir were judged most potent.

The development of antiviral *resistance* is a concern with long-term nucleoside/nucleotide treatment. Some 14 to 32% of patients who initially respond to lamivudine develop drug resistance within the first year of therapy and resistance increases to about 80% after 5 years of treatment;[29] lamivudine is therefore generally not recommended as first-line treatment.[30] Adefovir dipivoxil showed no resistance after 1 year of treatment, but the rate increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively.[19,20,31,32] Long-term therapy with

adefovir dipivoxil resulted in the development of resistance mutations in less than 6% of patients and it was effective in patients who had previously developed resistance to lamivudine.[20] Entecavir showed negligible resistance up to 6 years of treatment in previously treatment-naive patients, although resistance is reported to be much higher (nearly 60% after 6 years) in patients with lamivudine-resistant disease.[29] The resistance rate with telbivudine is reported to be 2 to 4% after 1 year of treatment,[33] and about 9% (in HBeAg-negative patients) to 21% (in HBeAg-positive cases) after 2 years.[29] Preliminary results also suggest negligible resistance at 48 weeks with tenofovir.[29] Combination therapy with different nucleoside and nucleotide analogues is being investigated in order to prevent drug resistance and improve efficacy.[29,34] The addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[16,35,36] The combination of lamivudine and adefovir was found to be as effective as lamivudine monotherapy.[37] The combination of lamivudine and telbivudine was less effective than telbivudine alone[38] but emtricitabine and adefovir was more effective than adefovir alone.[37]

While the AASLD[12] states that all the approved treatments may be given as initial therapy, their preferred *choice* is peginterferon alfa or the nucleoside analogues tenofovir or entecavir, in adults with HBeAg-positive or -negative chronic hepatitis B. In children with HBeAg-positive chronic hepatitis B, standard interferon alfa or lamivudine are recommended. In patients who are HBeAg-positive interferon is given for a defined duration (interferon alfa is given for 4 months and peginterferon alfa for 12 months), while a nucleoside/nucleotide analogue is usually given for an additional 6 months after HBeAg seroconversion. Most patients who are HBeAg-negative will relapse after treatment is stopped. In these patients interferon is also given for a defined duration (both interferon and peginterferon alfa are given for 12 months), but treatment with a nucleoside or nucleotide analogue is indefinite. Patients who have not responded to interferon alfa (standard or pegylated) therapy may be re-treated with a nucleoside analogue. Those who fail to respond after 6 months treatment should be switched to an alternative regimen. Adefovir[30,39] or tenofovir[39] may be given with lamivudine in those patients with lamivudine-resistant hepatitis B virus. Interferon alfa is not recommended in patients with compensated cirrhosis as it may cause hepatitis flares and hepatic decompensation. Guidelines are also available for other countries.[7,40-43]

Hepatitis B patients co-infected with **hepatitis D virus** are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[44] with high-dose interferon alfa (9 million units) given 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[45]

Treatment of chronic hepatitis C aims to decrease viral replication or eradicate hepatitis C virus, delay the progression to cirrhosis, and thereby decrease the frequency of hepatocellular carcinoma, and to treat extrahepatic complications of infection. The first available treatment was *interferon* alfa-2b, and this was followed by interferon alfa-2a, given subcutaneously 3 times a week. Patients treated with these interferons had a 10 to 20% chance of obtaining a sustained virological response (SVR), but had a high relapse rate. The combination of daily oral *ribavirin* with non-pegylated interferon alfa improved the rate of SVR after 48 weeks of treatment to about 40%. Further improvements in the SVR rates to about 60% have been reported since the introduction of weekly subcutaneous peginterferon alfa given with daily oral ribavirin. Studies[46,47] have found peginterferon alfa and ribavirin (SVR of 54 to 56%) to be more effective than interferon alfa and ribavirin (SVR of 44 to 47%). Factors predictive of a poor SVR are viral genotype 1, a high pretreatment viral load, increased bodyweight, and the presence of cirrhosis. A study[46] with peginterferon alfa-2b or interferon alfa-2b and ribavirin showed an SVR of 42% in patients with genotype 1, compared with about 80% in patients with genotypes 2 and 3. Furthermore, patients infected with hepatitis C virus genotype 1 require treatment for 48 weeks with the standard dose of ribavirin (1 or 1.2 g daily) compared with 24 weeks of ribavirin 800 mg daily in those infected with genotypes 2 or 3.[48] Other studies[49-53] suggest that SVR can be achieved in some patients infected with genotypes 2 and 3 with a 12 to 16 week course of treatment. This is particularly true for patients in whom hepatitis C virus RNA is undetectable after 4 weeks of treatment. In patients with genotype 1 infection, longer durations of therapy (up to 72 weeks), may be appropriate in slow responders (patients who achieved a 2 log fall in the viral load but in whom viral RNA is still detectable by week 12).[54,55] In one study,[54] a SVR rate of 44% was reported for slow responders who continued treatment for 72 weeks, compared with a SVR rate of 28% in those who received 48 weeks of treatment.

Detailed guidelines have been produced in the UK,[8,56-58] Canada,[59] and in the USA[5,60] for the management of chronic hepatitis C. They all recommend weekly subcutaneous peginterferon alfa plus daily oral ribavirin as the first choice of treatment in patients with moderate to severe chronic hepatitis C. The decision to treat those with mild chronic hepatitis should be individualised; if treatment is given, subcutaneous peginterferon alfa plus oral ribavirin is again preferred.

For genotype 2 and 3 infection, 24 weeks of treatment is usually recommended[5,56] but some[8,60] suggest that 12 or 16 weeks of therapy may be sufficient in patients with genotypes 2 and 3 with undetectable viral RNA at week 4. For genotype 1, treatment for 48 weeks is generally recommended. An early prediction of treatment failure in patients with genotype 1 infection is detectable hepatitis C virus RNA with less than a 2-log fall in viral load after 12 weeks of treatment. Some[5,8,57] suggest that stopping treatment in these patients may be considered at this point, while the British Society for Gastroenterology[56] recommends stopping treatment after 24 weeks if hepatitis C virus RNA is still detectable. Some guidelines[5,8] suggest re-treatment (with peginterferon and ribavirin) of nonresponders and relapsers who have significant fibrosis or cirrhosis and who initially received (non-pegylated) interferon with or without ribavirin[5,8] or monotherapy with pegylated interferon.[5] Patients with other genotype infections should be treated with combination therapy for 48 weeks.[57,60]

Thymalfasin is being investigated as an adjunct to conventional therapy for the treatment of chronic hepatitis B and C. Telaprevir[61-63] and boceprevir,[28,64-66] specific inhibitors of hepatitis C virus serine protease, have been developed and are used as adjuncts to conventional therapy in the treatment of chronic hepatitis C genotype 1.

Treatment of chronic hepatitis in HIV co-infected patients. HIV infection reduces the efficacy of current therapies for **hepatitis B**; it decreases response to interferon alfa and increases the incidence of lamivudine-resistant hepatitis B mutations.[1] Guidelines for the management of HIV and hepatitis B co-infection have been developed by various expert groups.[67-69] The British HIV Association guidelines[67] discuss appropriate choice of antivirals and their activity against hepatitis B virus and HIV. In patients not requiring HIV therapy, hepatitis B treatment should be with drugs that have no anti-HIV activity. *Peginterferon alfa* for 12 months is considered suitable for HBeAg-positive patients with minimal fibrosis, raised ALT, low hepatitis B virus DNA, and genotype A (if tested). Treatment should be stopped if there is no hepatitis B virus DNA response (less than 1 log reduction at 12 weeks and more than 2000 international units/litre at 24 weeks). Long-term treatment with *adefovir dipivoxil* may be given as an alternative to interferon therapy and is the drug of choice in patients with significant fibrosis. Adefovir dipivoxil may be given with *telbivudine*, but telbivudine should not be used alone because of the high rate of hepatitis B viral resistance. Starting a HAART regimen (including tenofovir and emtricitabine) early may be considered for antiretroviral-naive patients with wild-type HIV. Patients who require both HIV and hepatitis B therapy may be given *tenofovir* alone or with either *lamivudine* or *emtricitabine*, as part of, or in addition to, their antiretroviral regimen. Lamivudine or emtricitabine should not be used as the only active drug against hepatitis B virus in a HAART regimen, in order to prevent the development of viral resistance. *Entecavir* may be given when tenofovir has to be stopped due to toxicity, but it must be given with a fully-suppressive HAART regimen.[67] Successful treatment of HIV with HAART may result in severe exacerbation of hepatitis B in co-infected patients.

Treatment of **hepatitis C** in HIV co-infected patients has been associated with an increased rate of adverse effects and reduced response rates. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[70-72] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[71,72] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[70] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[70,72] Guidelines for the treatment and management of HIV and hepatitis C co-infection have been developed by various expert groups.[5,8,67,73] In general, they all recommend combination therapy with *peginterferon alfa* and *ribavirin*, usually for 48 weeks. Virological response should be reassessed at weeks 4 and 12 and treatment should only be continued beyond 12 weeks in those with an early virological response. Shorter periods of treatment (24 weeks) may be considered in patients with genotypes 2 or 3 infection who have a rapid virological response (response within 4 weeks). Patients with genotype 1 and 4 who have no virological response at 4 weeks but response at 12 and 24 weeks may be given a longer treatment course of 60 to 72 weeks. Significant haemolytic anaemia may occur with ribavirin, and therefore concurrent use with zidovudine should be avoided and when possible stavudine should be replaced. Didanosine should never be given with ribavirin due to potentially life-threatening complications, such as lactic acidosis, myopathy, neuropathy, pancreatitis, and steatosis.[67,73,74] Abacavir with ribavirin should be avoided if possible. If efavirenz is given with interferon the patient should be carefully monitored for increased CNS toxicity.[67]

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Herpesvirus infections

Established herpesvirus pathogens discussed below include Cercopithecine herpesvirus 1 (below), CMV (below), Epstein-Barr virus (p. 955.1), herpes simplex virus (p. 955.2), and varicella-zoster virus (p. 956.2). Herpesviruses 6, 7, and 8 have also emerged as potential pathogens and have been associated with a variety of disorders including childhood febrile illnesses, various malignancies including Kaposi's sarcoma (p. 718.1), and multiple sclerosis (p. 996.3).

Cercopithecine herpesvirus 1 infections. *Cercopithecine herpesvirus 1* (herpesvirus simiae, monkey B virus, herpes B virus) is a herpesvirus that usually infects macaque monkeys, but may rarely be transmitted to man by laboratory accidents or bites or scratches from infected monkeys. Initial symptoms and signs may include vesicles at the site of the bite or scratch, fatigue, fever, headache, and myalgia. Lymphadenitis or lymphadenopathy, abdominal pain, nausea, and vomiting may occur. As the infection spreads to the CNS there is increasing neurological involvement that can lead to encephalitis, coma, and death. Those patients who survive usually have serious neurologic impairment.

Initial **treatment**[1-3] should be prompt with thorough cleaning of the wound or exposure site. Intravenous high-dose *aciclovir* or *ganciclovir*, followed by oral therapy, is recommended for symptomatic or culture-confirmed infection. Ganciclovir is recommended in patients who have signs or symptoms of peripheral nervous system or CNS involvement. Routine **prophylactic** use of antivirals is not recommended, although postexposure prophylaxis with oral *valaciclovir* started within a few hours of exposure and given for 14 days may be considered for potential exposures. Vaccines against the virus have been investigated.

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Cytomegalovirus infections. Cytomegalovirus (CMV) is a member of the herpesvirus group. Infection may be by intra-uterine, perinatal, or sexual transmission, by oral contact with the saliva of infected individuals, by blood transfusion, or by transplantation of infected tissue. After infection, viral DNA becomes incorporated into the host cell DNA where it persists, with occasional reactivation, for the life of the individual. Primary infections in immunocompetent adolescents and adults are generally asymptomatic, although they may occasionally present as infectious mononucleosis, lymphocytosis, or lymphadenopathy. Most congenitally infected infants are also asymptomatic, but some may present with intra-uterine growth retardation, jaundice, hepatosplenomegaly, encephalitis, and thrombocytopenia. Conversely, CMV is a major cause of morbidity and mortality in immunocompromised persons, particularly transplant recipients and patients with AIDS where it may present as CMV retinitis, colitis, oesophagitis, hepatitis, pneumonitis, or neurological disease in the form of dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy. Pneumonitis is more common in transplant recipients while retinitis is most frequent in AIDS patients.

Treatment for CMV disease is usually only given to immunocompromised patients, in whom relapses are likely to occur after treatment is stopped due to the latent nature of the virus. Ganciclovir and its oral prodrug valganciclovir are used in the treatment of severe infections in transplant recipients and patients with AIDS but ganciclovir may cause neutropenia. Foscarnet is an alternative to ganciclovir with similar efficacy and does not produce myelosuppression, although nephrotoxicity and electrolyte disturbances are common. Cidofovir may also be used for the treatment of CMV retinitis, and has the advantage of intermittent use. However, long-term treatment may be limited by renal toxicity.

HIV-infected patients. US guidelines[1] for the **initial treatment** of *CMV retinitis* in HIV-infected adults and adolescents recommend, for immediate sight-threatening lesions, intravitreal injections of ganciclovir along with oral valganciclovir. For patients with peripheral retinal lesions, oral valganciclovir alone is recommended. Alternatives are intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, or intravenous cidofovir. For HIV-infected children, intravenous ganciclovir is recommended; intravenous foscarnet is an alternative and valganciclovir with or without an intraocular ganciclovir implant may be considered for children old enough to be given an adult dose of oral valganciclovir.[2]

After induction therapy, **maintenance therapy** (secondary prophylaxis) is recommended in AIDS patients with CMV retinitis until immune reconstitution as a result of antiretroviral therapy has been achieved or for life if it is not. The drug of choice is oral valganciclovir; alternatives include intravenous ganciclovir with or without foscarnet, intravenous foscarnet, or intravenous cidofovir.[1] Maintenance therapy may be stopped in patients with inactive CMV disease who have an increase in CD4+ T lymphocyte count to more than 100 cells/microlitre sustained for 3 to 6 months or more, although continued ophthalmic monitoring should be performed. Maintenance therapy should begin again if the CD4+ T lymphocyte count falls below 100 cells/microlitre.[1]

Early **relapse** of CMV retinitis in patients with persistent immunodeficiency is common and is generally due to poor penetration of drugs into the eye when given systemically, rather than drug resistance. Hence, re-induction and maintenance treatment with the same systemic drug used initially is recommended in patients who relapse after systemic treatment. An alternative drug should only be considered if drug resistance is suspected or toxicity precludes use of the initial drug. Combined ganciclovir and foscarnet may be considered for patients who are not suitable for other alternatives, but is associated with greater toxicity. Relapse later in therapy is usually due to drug resistance and patients with high-level ganciclovir-resistant isolates should be switched to an alternative therapy.[1]

In HIV-infected adults and adolescents, *CMV colitis* or *oesophagitis* should be treated initially with intravenous ganciclovir or foscarnet, or with oral valganciclovir.[1] Chronic maintenance therapy is not routinely recommended but should be considered if relapse occurs. For *neurological* disease, starting therapy promptly is critical for an optimal clinical response. Combination treatment with intravenous ganciclovir and foscarnet is currently favoured. The optimal duration of therapy has not been established.[1] Treatment of CMV *pneumonitis* is usually reserved for patients with cytological or histological evidence of CMV disease who do not respond to treatment for other pathogens; treatment is usually with intravenous ganciclovir or foscarnet. The role of maintenance in these patients is yet to be established.[1]

In HIV-infected adults and adolescents, *primary prophylaxis* with oral valganciclovir is not usually recommended because of the cost, the potential to induce CMV resistance, and the lack of proven survival advantage.[1]

Transplant recipients. Primary **prophylaxis** of CMV disease in high-risk patients, particularly transplant recipients, has been reported using intravenous ganciclovir,[3-5] valganciclovir,[6,7] foscarnet,[8] valaciclovir,[9-13] and CMV immunoglobulins.[14,15] Oral ganciclovir has also been used for primary prophylaxis and for *pre-emptive therapy* (treatment when active CMV infection is documented but disease has not yet been evident) in some transplant patients.[16-18] A systematic review[19] found that giving CMV immunoglobulins did not reduce the risk of CMV disease or all-cause mortality in solid organ transplant recipients and adding them to aciclovir or ganciclovir was not more effective than an antiviral given as monotherapy.

The British Transplantation Society (BTS)[20] and other expert groups, including an international consensus group of the Transplantation Society,[21] have published recommendations for the prevention and management of CMV disease after *solid organ transplantation*. These recommend that the highest risk patients, such as CMV-seronegative recipients of a solid organ transplant from a seropositive donor, should be offered primary prophylaxis. The following options are available in the UK and are recommended by the BTS:[20]

- oral valganciclovir for 100 days (in heart, kidney, kidney/pancreas, or liver transplant recipients)
- valaciclovir for 90 days (heart, kidney, kidney/pancreas, liver, or lung)
- intravenous ganciclovir for at least 28 days (heart, kidney, kidney/pancreas, liver, or lung)
- high-dose oral aciclovir for 12 weeks (kidney)
- intermittent CMV hyperimmune globulin for 12 weeks (kidney)

Frequent monitoring and possible pre-emptive treatment, usually with intravenous ganciclovir, may also be required.[20]

The above regimens are also used to prevent CMV disease when the donor and recipient are both CMV-seropositive and the patient is being treated with antithymocyte globulin, antilymphocyte immunoglobulin, or muromonab-CD3. If these drugs are not used, the BTS considers that no prophylaxis is needed for CMV-seropositive recipients of kidney, kidney and pancreas, liver, or heart transplants from seropositive donors; lung transplant recipients should be given chemoprophylaxis as for seronegative patients above.[20]

The BTS also recommended oral ganciclovir for 90 days as an option for prophylaxis after heart, kidney, kidney/pancreas, liver, or lung transplant, but acknowledged in their recommendations that, during their preparation, the UK manufacturer ceased production of oral ganciclovir; it was, however, retained as an option in the recommendations in case of availability in the future.[20]

Recommendations have also been produced for the management of CMV infection in recipients of allogeneic

stem cell transplantation by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation.[22] For treatment of CMV pneumonia, normal immunoglobulin is given with ganciclovir, but normal immunoglobulin is not required in other forms of CMV disease.[22] For prevention of CMV disease, pre-emptive therapy with either intravenous ganciclovir or foscarnet rather than primary prophylaxis, is the recommended approach. Intravenous ganciclovir is, however, effective for primary prophylaxis but should be reserved for patients at high risk of developing disease. Aciclovir or valaciclovir may also be used for primary prophylaxis but their use must be combined with monitoring and pre-emptive therapy with either intravenous ganciclovir or foscarnet. If, however, ganciclovir has been given for primary prophylaxis then foscarnet should be used for first-line pre-emptive therapy. The use of valganciclovir for primary prophylaxis is under investigation, but if it is given then foscarnet should be used subsequently for first-line pre-emptive therapy. Cidofovir may be used as second-line pre-emptive therapy.[22]

CMV vaccines are currently in development.

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Epstein-Barr virus infections. Epstein-Barr virus (EBV) is a DNA virus of the herpesvirus group occurring worldwide. EBV is the causative agent in infectious mononucleosis and many people acquire a non-symptomatic infection, frequently in childhood. After primary exposure the individual becomes a lifelong carrier of the virus. Chronic EBV infection, particularly in immunocompromised individuals, is associated with several malignant diseases including Burkitt's lymphoma, nasopharyngeal carcinoma, lymphoproliferative diseases, Hodgkin's disease, T-cell lymphomas, and some gastric cancers. EBV is also associated with chronic interstitial pneumonitis in infants with AIDS and with oral hairy leucoplakia and CNS lymphomas in older AIDS patients.

Infectious mononucleosis (glandular fever) is an acute, self-limiting, lymphoproliferative infection that is seen when primary infection occurs in adolescents or young adults.[1,2] Transmission is by intimate oral contact and the incubation period ranges from 30 to 50 days. Illness is characterised by fever, sore throat, and lymphadenopathy. Other signs and symptoms include malaise, myalgias, jaundice, rash, and hepatosplenomegaly. Symptoms may last for about 2 to 3 weeks and most patients recover uneventfully with only supportive treatment, although fatigue may continue for some months. Complications, including encephalitis, anaemias, or cytopenias, may occur in a few patients but are rarely fatal. Very rarely the illness may become chronic. Chronic active EBV is defined as severe illness lasting longer than 6 months, evidence of major organ involvement, and elevated titres of antibody to EBV. Prognosis in these patients is poor and many die due to progressive pancytopenia and hypogammaglobulinaemia, or lymphomatous disease.

There is no specific **treatment** for EBV infections[1] although various experimental approaches have been investigated.[3] Treatment is generally symptomatic: hydration, paracetamol or NSAIDs, and throat lozenges or sprays. A meta-analysis[4] of five randomised controlled studies involving 339 patients with mild, moderate, or severe EBV infection, found that patients who took aciclovir had less oropharyngeal shedding, but clinical benefit was marginal and not sustained on stopping treatment. In a small number of patients with chronic active EBV, ganciclovir[5,6] and interferons[7,8] appeared to have a beneficial effect on symptoms or EBV replication. Corticosteroids are generally not indicated in uncomplicated EBV infection[9] but may be useful in patients with airways obstruction.[1,10] They may also be considered in systemic complications such as autoimmune haemolytic anaemia, aplastic anaemia, and thrombocytopenia and some also consider that they may be used for CNS involvement, myocarditis or pericarditis. However, concern has been expressed that they may impair immunity, resulting in a larger reservoir of latent virus and thereby potentially increasing the risk of developing EBV-related tumours in later years.

Concurrent throat infection with streptococci should not be treated with amoxicillin or ampicillin since they may cause a maculopapular rash in patients with infectious mononucleosis.

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Herpes simplex infections. Herpes simplex virus (HSV, herpesvirus hominis) is a DNA virus belonging to the herpesviridae family and occurs worldwide.[1] HSV can be divided into serotypes HSV-1 and HSV-2. Both viruses establish chronic infection of sensory nerve ganglia from where they may be reactivated by triggers such as stress, bacterial infection, fever, irradiation (including sunlight), menstruation, and immunosuppression. The primary infection may therefore be followed by recurrent episodes in the same area.

Primary HSV infection is acquired through direct contact with lesions or mucosal secretions of persons with active HSV lesions or persons shedding virus asymptomatically. Primary HSV-1 infections usually occur in the perioral area, and HSV-2 in the genital area, but infection may be acquired at other sites, including the fingers (whitlow), and rectum (herpes proctitis) after anal intercourse. The incubation period for both viruses ranges from 2 to 12 days and most primary HSV infections are asymptomatic.

- HSV-1 commonly causes symptomatic *oropharyngeal herpes* presenting as acute gingivostomatitis or pharyngitis and characterised by lesions of the buccal and gingival mucosa, fever, and cervical adenopathy.
  HSV-1 infections are common among immunocompromised patients, especially organ transplant recipients and those undergoing chemotherapy. In these patients infection may be more severe with extensive mucocutaneous and disseminated disease.
- *Genital herpes* is characterised by a painful ulcerative rash, and may be accompanied by dysuria, vaginal or urethral discharge, and tender inguinal lymphadenopathy. Genital herpes is most commonly caused by HSV-2 but may also be caused by HSV-1. Genital herpes tends to be more extensive when caused by HSV-2 and may include complications such as aseptic meningitis, disseminated disease, extragenital lesions, and bacterial superinfection.
  Herpes lesions are common among HIV-positive patients and may be severe, painful, and atypical; HSV recurrences and asymptomatic shedding are also increased.
- *Ocular herpes* is generally caused by HSV-1. It usually affects only one eye and most often occurs on the cornea resulting in epithelial or stromal keratitis. Epithelial keratitis usually heals without scarring whereas stromal keratitis infection involves the deeper layers and may lead to scarring, loss of vision, and occasionally blindness. Less commonly, HSV may also cause uveitis, chorioretinitis, or acute necrotising retinitis.
- HSV has been identified as one of the commonest causes of Bell's palsy and acute, sporadic viral *encephalitis*. Both HSV-1 and HSV-2 may cause encephalitis and if left untreated it is often fatal or may result in neurologic sequelae, especially in those over 35 years of age.
- *Neonatal herpes* may result from transmission of HSV-2 (or HSV-1) from mother to child during the perinatal period. Risk of neonatal herpes is highest when the mother develops primary genital herpes near the time of delivery whereas risk is much reduced with recurrent episodes. Neonatal herpes is a severe disseminated infection and often results in CNS disease. Untreated it is often fatal and survivors often have persistent ocular disease.

Recurrent herpes results from **reactivation** of latent infection and is usually milder and the duration is shorter than the primary infection. Reactivation is frequently associated with prodromal signs and symptoms, ranging from a mild tingling sensation to shooting pains. Systemic symptoms and lymphadenopathy are rare. *Herpes labialis*, also known as fever blisters or cold sores, are the most common infection resulting from reactivation of HSV-1. Recurrence of genital herpes is more likely with HSV-2 than HSV-1 infections.

Management. The most widely used antiviral for herpes simplex infections is aciclovir. Alternatives with improved bioavailability include famciclovir and valaciclovir. Antiviral treatment of primary herpes simplex infections, while relieving symptoms and reducing the duration of viral shedding, does not prevent recurrences. Antiviral therapy is generally more effective for primary infections than for recurrences, and should be given as early as possible during the course of an active infection, preferably within 3 days of the onset of symptoms. Resistance to aciclovir is emerging, mainly in immunocompromised patients.[2] Herpes simplex vaccines have also been tried but with generally disappointing results.

- **Orofacial herpes simplex infection.** Primary mucocutaneous HSV infection can be treated with topical, oral, or intravenous aciclovir. Oral famciclovir and valaciclovir have similar efficacy to oral aciclovir and are recommended alternatives.[1] Mucocutaneous HSV in HIV co-infected patients may be treated with intravenous or oral aciclovir, oral famciclovir, or oral valaciclovir.[3] Recurrent episodes of herpes labialis are usually self-limiting and rarely require antiviral therapy. In immunocompetent patients careful hygiene, symptomatic treatment with analgesics, and the use of antiseptics to reduce secondary infection will usually suffice. The use of sunscreens may also reduce the frequency of recurrences. If antivirals are used they should be started early in the prodromal phase. Topical antivirals, including aciclovir, penciclovir, and tromantadine, have been used and are most effective when started during the prodromal phase.[4] Docosanol may be a further alternative for topical use.[5] Oral antivirals (aciclovir, famciclovir, and valaciclovir) may shorten the duration of symptomatic lesions by about 1 day.[4] High-dose oral valaciclovir has also been reported to be effective for suppression of recurrences and may provide the convenience of single-day treatment.[6] In immunocompromised patients with primary symptomatic infection or recurrent episodes of infection, intravenous or oral aciclovir, oral famciclovir, or valaciclovir may be used. An oral antiviral (aciclovir, famciclovir, or

valaciclovir) is recommended for patients with herpes labialis and concurrent HIV infection.[3]

- **Genital herpes** is usually treated with oral aciclovir, famciclovir, or valaciclovir.[3,7-9] Intravenous aciclovir is given for severe disease or neurological complications. A study[10] found that both oral aciclovir and oral valaciclovir were effective in suppressing the frequency of recurrences and amount of HSV shedding. However, treatment of the primary HSV infection appears to have no effect on subsequent recurrences. Symptomatic recurrences in patients with a recognisable prodrome may be aborted or the severity reduced by episodic treatment with a 5-day course of oral aciclovir, famciclovir, or valaciclovir begun by the patient.[7-9] Alternative regimens (for HIV-negative patients) include high oral doses of aciclovir for 2 days,[7,8,11] famciclovir for 1 day, or valaciclovir for 3 days.[7,8]

  In HIV-negative patients without a prodrome, or those with frequent recurrences, continuous suppressive therapy with aciclovir, famciclovir, or valaciclovir should be considered.[7-9] Once-daily suppressive therapy with valaciclovir was found to significantly reduce the risk of transmission of genital herpes among heterosexual, HSV-2-discordant couples.[12]

  Symptomatic HSV recurrences in HIV-positive patients respond more slowly to anti-HSV treatment and longer treatment courses and higher doses of antivirals are needed.[8,13] Suppressive or episodic therapy should be considered for all HIV-infected persons.[3,7,13]
- **Ocular herpes simplex infections** usually require treatment with antivirals and/or interferons. Topical antivirals include aciclovir, brivudine ganciclovir, and trifluridine; these have similar efficacy and are more effective than idoxuridine or vidarabine.[14] Systemic antivirals include aciclovir, famciclovir, and valaciclovir. Other systemic antivirals that have been evaluated are ganciclovir, foscarnet, and cidofovir.[14] HSV epithelial keratitis can be treated with a topical antiviral, a topical interferon (alfa or beta), or a combination of both. Benefit appears to be similar after 7 days of treatment with either an interferon or antiviral monotherapy, but combination therapy with interferon and an antiviral produces faster healing than a topical antiviral alone.[14] Trifluridine eye drops are the treatment of choice for herpes simplex epithelial keratitis in HIV-infected patients.[15]

  Topical corticosteroid monotherapy is contra-indicated for epithelial keratitis as disease severity can be increased; however, the treatment for stromal keratitis does consists of both topical trifluridine and topical corticosteroids. The Herpes Eye Disease Study[16] reported that the addition of topical prednisolone to trifluridine reduced the risk of persistent or progressive stromal kerato-uveitis by 68%, while the further addition of oral aciclovir provided no additional benefit.[17] Stromal keratitis or iritis was not prevented by the addition of oral aciclovir in patients with epithelial keratitis and currently receiving topical trifluridine.[18] Oral aciclovir, however, was effective in reducing the rate of recurrent HSV ocular disease, particularly in patients with prior stromal keratitis,[19] and may be of benefit to patients in uveitis when added to topical corticosteroid and antiviral therapy.[20]
- **Severe or disseminated herpes simplex infections,** particularly in immunocompromised patients, require intravenous therapy. Aciclovir is given for CNS infections and disseminated HSV infections.[1,3,15] Intravenous foscarnet is recommended for infections resistant to aciclovir; intravenous cidofovir is an alternative.[3] Prolonged applications of topical trifluridine, cidofovir, or imiquimod also have been used successfully for lesions on external surfaces.[3] Neonates with evidence of herpes infection should be given high-dose intravenous aciclovir.[7,9,15] Immunocompromised patients with frequent or disabling recurrences may benefit from prophylactic oral aciclovir, valaciclovir, or famciclovir.[3,15]

Prevention. Intravenous aciclovir is recommended for all HSV-seropositive patients undergoing allogeneic haematopoietic stem cell transplants to prevent reactivation of latent HSV. Aciclovir may also be considered for HSV-seropositive patients undergoing autologous haematopoietic stem cell transplantation who are at risk of developing severe mucositis from the conditioning chemotherapy.[21] Oral aciclovir, famciclovir, or valaciclovir may be given to patients who can tolerate oral therapy. A systematic review[22] of interventions for the prevention and treatment of HSV in patients being treated for cancer found aciclovir to be effective; valaciclovir was found to be no more effective than aciclovir and high doses of valaciclovir were no better than low doses. There is a risk of neonatal herpes in the infants of mothers with genital herpes infection. Although clinical studies have shown that oral aciclovir or valaciclovir used near term reduce viral shedding and recurrence at labour and birth and the use of caesarean section these studies were not sufficiently powered to determine if they reduce the occurrence of neonatal herpes.[23,24] Prophylactic use of antivirals in late pregnancy is therefore not routinely recommended.[15]

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Varicella-zoster infections. Varicella-zoster virus (VZV) belongs to the herpesviridae and causes 2 separate diseases: chickenpox (varicella) and herpes zoster (zoster, shingles). Infection may be acquired through the respiratory tract via airborne droplets or by close contact with infected individuals. Primary infection with VZV usually occurs in childhood and results in chickenpox. In immunocompetent persons chickenpox is self-limiting and results in lifelong immunity. However, the virus is not eliminated and remains dormant within sensory nerve ganglia. In later life or in immunocompromised persons, reactivation of the virus from the sensory nerve may occur and give rise to nerve pain and a dermatomal rash (herpes zoster). Immunocompromised patients may develop a second episode of chickenpox.

The incubation period for *chickenpox* is about 14 to 15 days. In children it usually presents with a generalised rash, fever, and malaise. The rash rapidly progresses from macules to papules and then to vesicular lesions before crusting, with successive crops appearing over several days. Chickenpox acquired in childhood is commonly a mild disease lasting 3 to 5 days, with secondary bacterial skin infections the commonest complication. Chickenpox in adults may be more severe, and have a higher incidence of complications. Immunocompromised individuals may develop severe chickenpox with multiple organ involvement, high fever, more extensive vesicular skin eruption, severe pneumonia, and encephalitis.

Primary varicella infection in the first 20 weeks of pregnancy has been associated rarely with congenital varicella syndrome, characterised by skin scarring, local muscular atrophy, chorioretinitis, encephalitis, cortical atrophy, and microcephaly. Maternal infection until at least 5 days before delivery may result in a mild neonatal infection, while maternal infection from 7 days before to 7 days after delivery may result in a severe infection of the neonate with a reported fatality of about 30%.

Herpes zoster is characterised by painful vesicular eruptions in a dermatomal distribution. It may be preceded by a prodromal phase with fever and malaise or pain over the affected dermatome. Lesions continue to form over a period of 3 to 5 days, and disappear, often with a degree of scarring, after 10 to 15 days. Chronic pain that may persist after the rash has healed is termed postherpetic neuralgia (p. 10.3) and occurs in about 10% of patients. Involvement of the trigeminal nerve can lead to sight-threatening ophthalmic herpes zoster. Herpes zoster may be more severe and extensive in immunocompromised patients but is rarely fatal.

Treatment. Recommendations for the treatment of *chickenpox* in children,[1] adults,[2] and during pregnancy[2,3] have been developed. Treatment in otherwise healthy patients is usually symptomatic using antipyretics, analgesics, and antipruritics and is aimed at reducing complications. Antibacterials may be required for secondary skin infections. Antivirals are not recommended for the treatment of uncomplicated chickenpox in otherwise healthy children.[1] However, oral aciclovir may shorten the duration of fever and the number of lesions when given within 24 hours of onset of symptoms.[4] Antivirals do not reduce the incidence of chickenpox-associated complications in otherwise healthy children but may be useful in adults or immunocompromised patients. Intravenous therapy may be used in severe chickenpox.

The place of antivirals in the treatment of *herpes zoster* is well established; recommendations and guidelines on management have been produced.[5-8] Antiviral treatment can reduce the severity and duration of acute pain, minimise complications and propagation of the rash, and reduce viral shedding.[5] Systemic antivirals are recommended for all immunocompetent patients who are over 50 years of age, have moderate to severe pain or rash, or have nontruncal involvement. Treatment should be started within 72 hours of the onset of the rash and is usually continued for 7 to 10 days. Antiviral therapy may also be considered in those presenting 72 hours after the onset of the rash when there are skin, motor, neurological, or ocular complications, when new vesicles are still forming, in the elderly, or in those with severe pain.[7] Topical antivirals are not recommended.

Aciclovir may be given orally or intravenously, depending upon the severity of the infection. Oral famciclovir, valaciclovir, or brivudine are alternatives.[7] Bioavailabilities of these drugs are better than aciclovir and they also appear to be superior in terms of healing lesions and equally or more effective in relieving pain.[7,9-12]

There has been controversy over the use of oral aciclovir to prevent **postherpetic neuralgia** and ocular complications. A meta-analysis suggested that treatment of herpes zoster with oral aciclovir within 72 hours of the onset of rash could reduce the *incidence* of residual pain at 6 months by 46% in immunocompetent adults.[13] Subsequent analyses found little[14] or no[15] evidence that aciclovir decreased the incidence of postherpetic neuralgia and none for a reduction in incidence with either famciclovir[14,15] or valaciclovir.[14] It is, however, generally agreed that antivirals do reduce the *duration* of postherpetic neuralgia[14] and some experts recommend antivirals even in patients at low risk for developing postherpetic neuralgia and other complications.[7] The addition of corticosteroids to antiviral therapy does not reduce the incidence or duration of postherpetic neuralgia, but may improve the rate of resolution of the neuritis or improve pain control.[16,17]

Severely **immunocompromised** patients or others at high risk of severe or disseminated herpes zoster should receive intravenous aciclovir. Oral aciclovir, famciclovir, or valaciclovir may be considered in less severely immunocompromised patients.[7] Sorivudine and brivudine are also effective against zoster infections.[18] Brivudine is as effective if not more, than aciclovir in immunocompromised patients[19] but is not recommended in such patients because of a potentially fatal interaction with fluorouracil (and related drugs).[7] Sorivudine has been withdrawn from the market after deaths in patients also taking fluorouracil. Foscarnet may be of value in aciclovir-resistant varicella-zoster infections[20-22] although treatment failures have been reported.[23]

Ophthalmic herpes zoster is treated with an oral antiviral, given within 72 hours of the onset of the rash; additional treatment with topical aciclovir to the eye may also be considered. Oral aciclovir, famciclovir, and

valaciclovir are all effective in reducing the pain associated with ophthalmic zoster.[24,25]

Prevention. Varicella-zoster immunoglobulins are used for the prevention of chickenpox in patients at high risk of developing complications, such as the immunocompromised, neonates whose mothers developed chickenpox 7 days before to 7 days after delivery, and in susceptible pregnant women after significant exposure. There have been reports of severe chickenpox occurring in patients undergoing corticosteroid therapy. In the UK, use of varicella-zoster immunoglobulins is recommended in persons exposed to the virus who have received high doses of corticosteroids within the previous 3 months[26] (see also Varicella, under Precautions for Corticosteroids, p. 1619.2).

Varicella-zoster vaccines are available in some countries and in the UK vaccination is recommended for active immunisation against chickenpox in persons considered to be at high risk of either infection or complications, including healthy contacts of immunocompromised patients. In the USA, a 2-dose vaccination regimen is recommended as part of the primary immunisation schedule of infants and children. Routine vaccination is also recommended for persons over the age of 13 years without evidence of immunity[27] and a high-potency vaccine against herpes zoster is recommended for persons 60 years of age and older.[28] For further discussion of varicella-zoster vaccines, see p. 2423.3.

Transmission of chickenpox to household contacts is not prevented by giving aciclovir to the primary case but there is evidence to suggest that transmission can be suppressed by giving aciclovir to susceptible contacts during the incubation period.[29,30] Although the need for such prophylaxis has been questioned, especially in otherwise healthy children,[31] prophylaxis or early treatment with antivirals may be useful for household contacts in whom the infection might prove to be more severe.[1,32,33]

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HIV infection and AIDS

The causative agent of AIDS (acquired immunodeficiency syndrome) is the human immunodeficiency virus (HIV; previously known as HTLV-III or LAV), a retrovirus transmitted by sexual contact, blood and blood products, the use of contaminated needles, or vertically from mother to fetus. Two subtypes of HIV have been identified. The most common is HIV-1, which occurs worldwide. HIV-2 is found mainly in West Africa and is associated with a slower progression to AIDS than HIV-1.

HIV uses the CD4 receptor and the CCR5 or CXCR4 co-receptors to enter T lymphocytes and monocytes/macrophages, where viral RNA is reverse transcribed into DNA and inserted into the host genome. Viral replication results in immune activation and progressive depletion of CD4+ T lymphocytes. Primary HIV infection is characterised by the development of non-neutralising HIV antibodies (seroconversion), and in some patients may manifest as a transient rash, sore throat, and lymphadenopathy (seroconversion illness). Primary HIV infection is usually followed by a largely asymptomatic chronic infection, during which persistent generalised lymphadenopathy may be noted. Chronic HIV infection is characterised by gradual depletion of CD4+ T lymphocytes resulting in progressive immunodeficiency. This may become clinically apparent when symptoms such as fatigue, weight loss, recurrent fever, diarrhoea, or thrush occur. Alternatively, patients may develop severe opportunistic infections such as pneumocystis pneumonia, toxoplasma encephalitis, oesophageal candidiasis, cryptococcal meningitis, CMV retinitis, *Mycobacterium avium* complex, recurrent bacterial pneumonia, pulmonary or extrapulmonary tuberculosis, or neoplasms such as Kaposi's sarcoma, cervical carcinoma, and lymphomas; these are collectively referred to as AIDS-defining illnesses. AIDS-defining illnesses generally do not occur until severe immunodeficiency is present (CD4+ T lymphocyte count of less than 200 cells/microlitre or less than 14% of the total lymphocyte count). Most AIDS-defining events can therefore be prevented if effective HIV treatment is started before the CD4+ count has fallen to this level. Since the availability of highly active antiretroviral therapy (HAART), the incidence of AIDS-defining illnesses has markedly declined. However, antiretroviral therapy may result in toxicity or paradoxical worsening of underlying opportunistic infections.

During the course of chronic HIV infection, measurement of the CD4+ count and HIV RNA (viral load) will aid prognosis. The absolute CD4+ count or CD4% reflects the susceptibility to opportunistic infections while a high HIV viral load is associated with a more rapid decline in CD4+ count and more rapid clinical disease progression. The HIV viral load is also used to monitor success of antiretroviral therapy, where the goal is complete suppression of viral replication (resulting in undetectable HIV viral loads). CD4+ counts and viral loads are both taken into consideration in the decision to start antiretroviral therapy.

TREATMENT

The following discussion relates to the use of antiretrovirals in HIV infection and AIDS. The treatment of secondary and opportunistic infections and other complications is covered under the relevant sections, below.

Treatment strategies for HIV infection are changing rapidly and frequently updated guidelines for the treatment of HIV infection are published for the USA,[1-3] for the UK,[4] by the European AIDS Clinical Society (EACS),[5] and by WHO.[6,7]

Data from clinical studies in support of treatment of *acute* HIV infection are limited. Treatment of the primary HIV infection may be beneficial in relieving symptoms due to HIV during the seroconversion illness; it may restrict damage to the immune system, reduce the viral load set point once treatment is stopped and reduce the rate of viral mutation and risk of HIV transmission to sexual partners.[8] The UK guidelines do not routinely recommend early treatment of acute HIV infection, but suggest that treatment may be considered in patients with neurological involvement, any AIDS-defining illness, or a CD4+ count less than 200 cells/microlitre for 3 months or more.[4] US guidelines[2] state that treatment of acute infection is optional.

In *chronic* infection, the goal of antiretroviral therapy is to prevent or reverse immunodeficiency, prevent opportunistic infections, and prolong survival. The decision of when to start antiretroviral therapy should be individualised to take into account patient-specific relative risks and benefits of treatment. Guidelines[1,2,4-6] recommend that antiretroviral treatment should be given to patients whose CD4+ counts have fallen below 200 to 350 cells/microlitre or who have symptomatic disease, irrespective of their viral load or CD4+ count. Treatment is generally not indicated for asymptomatic patients with a CD4+ count greater than 350 cells/microlitre but may be considered for patients with a high viral load (more than 100 000 copies/microlitre), rapid CD4+ count decline (more than 100 to 120 microlitres per year), co-infection with hepatitis B or C virus, HIV-associated nephropathy, or risk factors for non-AIDS diseases, particularly cardiovascular diseases.[2,4] However, some experts in the USA[1] recommend antiretroviral treatment should be given to asymptomatic patients with CD4+ counts of 500 cells/microlitre or less and that it should also be considered in those with CD4+ counts above 500 cells/microlitre.

Combination therapy with antiretroviral drugs aims to improve potency, minimise toxicity, and delay drug resistance. The drugs used in combination therapy are:

- nucleoside reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine, and zidovudine) or the nucleotide reverse transcriptase inhibitor tenofovir
- HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir)
- non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine, and etravirine)
- the entry inhibitors, including the HIV-fusion inhibitor enfuvirtide, the CCR5-antagonist maraviroc, and the HIV-integrase inhibitors dolutegravir, raltegravir, and elvitegravir

Although ritonavir inhibits HIV-protease when given in high doses, it is almost exclusively used in low doses for its CYP450 inhibitory properties, to boost the plasma concentrations of co-administered HIV-protease inhibitors. Combination of three antiretrovirals, typically two nucleoside/nucleotide reverse transcriptase inhibitors (NsRTI/NtRTI) plus either a (ritonavir-boosted) HIV-protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), is referred to as ***highly active antiretroviral therapy*** (***HAART***). Such regimens have produced sustained reductions in viral load often to levels below the limit of detection, and have been associated with improvements in CD4+ count, immune function, and clinical well-being. This is reflected by the decline in morbidity and mortality among patients with HIV infection since the availability of HAART. Triple therapy regimens, consisting of at least 2 classes of antiretrovirals, are superior to monotherapy, dual therapy, or triple NRTI therapy. Quadruple therapy regimens may be of benefit in some patients but are likely to increase toxicity. Complete suppression of viral replication minimises the emergence of drug-resistant HIV.[9-11]

When considering combination antiretroviral therapy several factors need to be taken into consideration. Drug combinations should provide additive or synergistic antiviral activity without increased toxicity or pharmacokinetic interactions that may affect the efficacy of co-administered drugs. Drugs with maximal potency should be combined so as to minimise the risk of drug resistance developing. The patient's ability to adhere to a regimen, comorbid conditions, results of genotypic drug resistance testing, and the likelihood of pregnancy should also be taken into consideration.

In the developed world the availability of co-formulations of zidovudine with lamivudine, abacavir with lamivudine, and tenofovir with emtricitabine, and concerns over the toxicity of stavudine and zalcitabine have resulted in most treatment-naive patients starting with one of these combinations. There has been a shift from zidovudine/lamivudine to abacavir/lamivudine or to tenofovir/emtricitabine because of concern over the adverse effects and long-term toxicity (lipoatrophy) associated with zidovudine. Some experts in the USA[2] consider abacavir/lamivudine to be a second-line combination because abacavir is associated with an increased risk of myocardial infarction in patients with high cardiac risk factors. Furthermore there is concern regarding the effectiveness of abacavir/lamivudine in patients with baseline viral loads more than 100 000 copies/microlitre.[1,2,4] Similarly, among the NNRTIs, delavirdine is now rarely used and a shift from nevirapine to efavirenz has occurred because of the potential of nevirapine to cause severe skin and liver toxicity. Efavirenz is the preferred NNRTI except for

pregnant women (especially during the first trimester) or women with a high pregnancy potential. A co-formulated tablet containing tenofovir, emtricitabine, and efavirenz is available and taken once daily. HIV-protease inhibitors are almost exclusively used with ritonavir boosting. Giving amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, or tipranavir, with ritonavir, improves the pharmacokinetic properties and clinical efficacy of these HIV-protease inhibitors. Acceptable PIs for treatment-naive patients are ritonavir-boosted atazanavir, darunavir, fosamprenavir, lopinavir,[1,2,4] or saquinavir.[2,4] Randomised, controlled studies indicate that triple NRTI treatment with zidovudine, lamivudine, and abacavir is less potent than combining two NRTIs with either an NNRTI or a PI, with higher rates of virological failure and its use is not recommended.[2,4] Triple or quadruple NRTI treatment regimens are not recommended,[1] but may be used in exceptional circumstances when a PI- or NNRTI-based HAART regimen cannot be given.[4] In the USA, raltegravir and two NRTIs, preferably tenofovir and emtricitabine, may also be given as an initial treatment regimen.[1,2] Maraviroc with zidovudine plus lamivudine was found to be as effective as efavirenz when used exclusively in patients with CCR5-tropic HIV infection; in this patient group maraviroc may be considered for treatment-experienced patients or if primary drug resistance is present.[1]

WHO guidelines[4] recommend that treatment-naive patients be started on a triple therapy regimen, consisting of two NRTIs and one NNRTI. Suggested regimens include zidovudine, lamivudine, and efavirenz or nevirapine, *or* tenofovir, lamivudine or emtricitabine, and efavirenz or nevirapine.

Treatment failure. Although HAART regimens are generally most effective in antiretroviral-naive patients, good responses can also be achieved in treatment-experienced patients.[1,2] In patients who have an inadequate response to therapy, adherence needs to be carefully assessed and reasons for potential non-adherence addressed. If a patient has drug toxicity, intolerance to therapy, or for any other reason is unable to adhere to therapy, a change of drugs should be considered. Change of treatment should also be considered if the patient has a suboptimal virologic response to their current antiretroviral therapy and may be considered in those with limited gains or decreases in their CD4+ count or clinical deterioration while on fully suppressive regimens. Resistance testing is needed to determine which antiretroviral drugs will possibly be the most active.

Choice of second-line regimen is essentially empirical, since there is limited evidence from controlled studies.[13] Addition of a single antiretroviral drug to a failing combination regimen is generally not recommended because further resistance may result.[1,2,4] When a new regimen is started, 2 to 3 drugs should be included to which the patient has not been exposed or to which the virus is not resistant.

- A failing regimen of two NRTIs and an NNRTI may be replaced by a ritonavir-boosted PI with one or two different fully active NRTIs.[1,2,4,6]
- In a failing NNRTI regimen, the NNRTI should be replaced with a drug with different mechanism of action, most commonly a ritonavir-boosted PI, but newer drugs such as the integrase inhibitor raltegravir, the CCR5 antagonist maraviroc, or the NNRTI etravirine may be tried. Etravirine must be given with a potent ritonavir-boosted PI-containing regimen.[1]
- For patients who fail on a ritonavir-boosted PI based regimen, treatment options are to change to a NNRTI-based regimen (if not previously used), substitute the HIV-PI for one with limited cross-resistance (such as ritonavir-boosted atazanavir, darunavir, lopinavir, or tipranavir), and/or add a drug with a different mechanism of action, such as the HIV-fusion inhibitor enfuvirtide, raltegravir, or the CCR5 antagonist maraviroc.[2,4]

In **multidrug-experienced patients** the goal of treatment is still to suppress HIV-1 RNA to less than 50 copies/mL. In these patients treatment regimens should include at least 2, and ideally 3, fully active drugs, and at least 1 drug from a different class, such as enfuvirtide, etravirine, maraviroc, or raltegravir, should be included.[1,4] Ritonavir-boosted PIs with activity against resistant viruses are usually the basis of a new regimen.[1,2] Ritonavir-boosted tipranavir[14,15] or darunavir,[16] when used as part of a combination regimen with at least one (preferably two) active agents such as enfuvirtide, result in better viral suppression and CD4+ count increases in patients with multidrug resistant HIV-1 infection than standard ritonavir-boosted PIs.[17,18] Etravirine, which may be used depending on the number of NNRTI-associated resistance mutations present, must be given with a potent ritonavir-boosted PI; darunavir, but not tipranavir, is suitable.[1] There is no evidence for the use of two HIV-PIs,[1] but some consider that they may be an alternative for patients with limited therapeutic options living in resource-limited countries, where the newer more expensive drugs are not available.[19]

While HAART maintains plasma viral load at undetectable levels in most patients, viral replication rapidly returns to pretreatment levels once treatment is stopped. *Treatment interruption* may be associated with a precipitous decline of CD4+ count, clinical disease progression, and the development of drug resistance. Structured long-term treatment interruptions (or planned breaks) are generally not recommended in patients with HIV infection, even if drug-resistance results in chronic non-suppression of HIV RNA.[1,2,4,20] The continued efficacy of any HAART regimen is dependent on strict adherence to treatment. The improved formulation and co-formulation of several antiretrovirals has reduced the pill burden and newer drugs tend to have fewer adverse effects. However, the cost of treatment is high and access to effective treatment in developing countries with high burdens of disease, although improving, remains limited.

Newer antiretroviral drugs to further reduce pill burden and limit toxicity are in development. In addition, research continues into further drugs with enhanced activity against resistant isolates, such as HIV-entry inhibitors (that inhibit the three steps of HIV entry: CD4 attachment, chemokine receptor binding, and membrane fusion) and HIV-integrase inhibitors.[21,22] Interleukin-2 may improve the CD4+ count in patients with advanced HIV infection, or preserve CD4+ counts in patients with early HIV infection. However, it is not clear that this results in any additional clinical benefit to patients on antiretroviral therapy (see p. 810.3). Some vaccines aimed at preventing HIV infection or reducing the HIV viral load are currently under investigation (see AIDS Vaccines, p. 2376.1).

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HIV-associated infections and complications. Infections. Patients with HIV infection and AIDS are at increased risk of specific bacterial, fungal, protozoal, and viral infections largely as a result of impaired cell-mediated immunity. With the introduction of antimicrobial prophylaxis and HAART there has been a significant decrease in the incidence of most AIDS-defining opportunistic infections, especially in the developed world. However, HIV-related opportunistic infections and deaths still occur in patients newly diagnosed with HIV infection, in those in the early course of HAART, in those non-adherent to their HIV treatment, or in those with drug-resistant HIV infection; deaths also result from non-opportunistic infections and chronic viral hepatitis.[1]

- Infections affecting the *lungs* include recurrent bacterial pneumonia (p. 200.1), pneumocystis pneumonia (p. 567.2), and pulmonary tuberculosis (p. 210.2).
- Many pathogens cause *gastrointestinal-tract disease* in HIV-infected patients, including candida oesophagitis (p. 564.1), CMV colitis (p. 954.2), and amoebiasis (p. 919.1), cryptosporidiosis (p. 921.1), giardiasis (p. 921.3), isosporiasis (p. 921.3), or microsporidiosis (p. 924.1).
- AIDS-defining *neurological* infections include AIDS dementia complex (HIV encephalopathy), cryptococcal meningitis (p. 565.2), cerebral toxoplasmosis (p. 924.2), and progressive multifocal leukoencephalopathy (see Infections in Immunocompromised Patients, p. 960.2).
- *Systemic* opportunistic infections in AIDS patients include tuberculosis, coccidioidomycosis (p. 565.1), histoplasmosis (p. 566.1), and *Mycobacterium avium* complex infections (see Nontuberculous Mycobacterial Infections, p. 194.1). CMV retinitis (p. 954.2) may be a cause of blindness, while chronic herpesvirus infections (p. 954.1) may affect the skin and gastrointestinal tract.

Recommendations have been published for both treatment and prophylaxis of opportunistic infections in AIDS patients.[2-4] Recovery of immune function in patients responding to HAART may be sufficient to protect against certain opportunistic infections and to allow primary or secondary prophylaxis to be stopped.

Other complications. Non-infectious complications of HIV infection include cardiovascular events, renal disease, metabolic and skeletal disorders, toxicities of HAART, and malignancies (p. 959.1).

HIV infection and adverse effects of HAART may accelerate the typical problems associated with ageing and in particular *cardiovascular disease*.[5] HIV infection appears to increase the risk of coronary heart disease by up to two-fold compared with uninfected persons and the mean age at which it develops is more than 10 years earlier (at about 50 years of age) in HIV-infected persons.

Black patients with HIV infection may develop chronic or end-stage *renal disease* due to HIV-associated nephropathy (HIVAN) or thrombotic microangiopathy; antiretroviral therapy can improve renal function in HIVAN and may slow or even stop its progression. Acute renal failure is common in hospitalised patients with (opportunistic) infections, malignancies, or hepatitis C co-infection, while proteinuria is common in all HIV patients and may reflect an increased risk of cardiovascular events. Antiretrovirals, in particular tenofovir and indinavir, may cause renal dysfunction.[6-9] Guidelines for the management of chronic kidney disease in HIV-infected patients have been developed by the HIV Medicine Association of the Infectious Diseases Society of America.[6]

Metabolic complications associated with HIV infection and HAART include dyslipidaemia, abnormal glucose metabolism (insulin resistance, impaired glucose tolerance, and diabetes mellitus), and bone disorders (osteopenia, osteoporosis, and osteonecrosis); hepatic steatosis may occur with or without lipodystrophy in the form of lipohypertrophy (fat accumulation) or lipoatrophy (fat loss). HAART may occasionally cause lactic acidosis.[10,11]

Pancytopenia is commonly seen in patients with advanced HIV infection, and *neurological syndromes* such as aseptic meningitis, headache, neuropathy, myopathy, and Guillain-Barré syndrome, may occur at any stage of the infection.

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HIV-associated malignancies. There is an increased incidence of certain malignancies in patients with HIV infection. Malignancies commonly associated with HIV infection are Kaposi's sarcoma (p. 718.1), Hodgkin's disease, non-Hodgkin's lymphoma and primary CNS lymphoma (see AIDS-related Lymphomas, p. 697.2), invasive cervical cancer (p. 704.2), and anal cancer (see Malignant Neoplasms of the Anus, p. 708.1). Some tumours may regress in response to effective antiretroviral therapy. Guidelines for the management of HIV-associated malignancies have also been issued by the British HIV association.[1]

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HIV-associated wasting. Severe malnutrition in HIV-infected patients is recognised as wasting syndrome[1-4] and has been defined as an involuntary loss of body-weight of 10% or more (of both lean and fat tissue) and may be associated with fatigue, fever, and diarrhoea (not explained by another cause). However, there is some debate as to whether it should be defined as the loss of 5 or 10% of usual weight and whether changes in body composition, rather than weight alone, better define the syndrome. Wasting is associated with morbidity and mortality in advanced HIV infection and AIDS. Wasting syndrome has been associated with inadequate oral intake, malabsorption syndrome, metabolic disorders, hypogonadism, and increased cytokine production. Weight loss and malnutrition tend to be less severe in patients taking HAART. However, loss of body cell mass may occur in patients given HAART and needs to be differentiated from fat redistribution (lipodystrophy).

Since HIV replication is central to the pathogenesis of wasting syndrome, antiretroviral therapy is indicated. Nutritional intervention, exercise, and drug treatment may be indicated in patients who have an incomplete response to antiretroviral therapy. Drugs that have been tried include growth hormone, the appetite stimulants dronabinol and megestrol, the growth hormone mediator mecasermin, steroid hormones (testosterone and testosterone analogues), synthetic anabolic steroids (nandrolone, oxandrolone, and oxymetholone), and drugs that decrease cytokine production such as pentoxifylline and thalidomide. A suggested initial approach to the management of wasting[3] is to increase dietary intake of protein or total calories. Nutritional supplementation and exercise should always be considered and encouraged before drug treatment is started. Testosterone replacement may be given to HIV-infected men with significant weight loss and low testosterone levels, and megestrol may be given to patients who are unable to voluntarily increase or maintain total energy intake. Other drug treatments such as growth hormone and anabolic steroids may be considered where rapid weight loss is associated with acute infection and in severe cases of continued weight loss refractory to non-drug therapies.

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HIV infection prophylaxis

Non-occupational exposure to HIV. Behavioural changes are the most effective methods of reducing the spread of HIV infection in the general population. These include the promotion of safe sex practices and needle exchange schemes for intravenous drug users. Guidelines have been published in the USA[1] for postexposure prophylaxis (PEP) after sexual activity, intravenous drug use, or other non-occupational exposure to HIV amongst the general population:

- a 28-day course of HAART is recommended for persons who have had non-occupational exposure to potentially infected body fluids of a person known or suspected to have HIV infection when there is a substantial risk of transmission and when the person presents within 72 hours of exposure
- for persons seeking care within 72 hours of non-occupational exposure from a person of unknown HIV status, or when such exposure would represent a substantial risk for transmission if the source were HIV-infected, it is recommended that risks and benefits of PEP be evaluated on an individual case basis
- PEP is generally not recommended for persons seeking care where there is no substantial risk for HIV transmission or for those presenting more than 72 hours after exposure (although it may be considered for persons seeking care after more than 72 hours if the exposure represents a substantial risk for transmission)

Guidelines for non-occupational PEP have also been produced in the UK[2,3] for exposure outside the healthcare setting and are similar to those for occupational exposures (see below); when given, PEP should be started as soon as possible after exposure.

Occupational exposure to HIV. The risk of seroconversion is estimated at about 0.3 to 0.4% after percutaneous contamination with HIV-infected blood and considerably less for accidents involving contamination of intact skin or mucous membranes. In view of potential toxicity of antiretrovirals, the decision whether to give PEP should balance the risk of infection against the potential drug toxicity and PEP should generally only be offered to intermediate to high-risk cases. Factors associated with increased risk of occupationally-acquired HIV infection include:

- deep injury
- visible blood on the device which caused the injury
- injury with a needle which had been placed in a source patient's artery or vein
- primary HIV infection or terminal HIV-related illness in the source patient

If PEP is given it should be started as soon as possible after the exposure. Zidovudine monotherapy has been extensively used for PEP and reduces seroconversion after percutaneous exposure by 79%. PEP with combination antiretroviral drugs is now preferred as it results in more complete suppression of viral replication and is more likely to afford some protection against drug-resistant HIV strains.

Guidelines for the UK[2] recommend a 4-week course of antiretroviral therapy after occupational percutaneous, mucous membrane, or broken skin site exposure to high-risk body fluids or tissues known to be, or suspected of being, infected with HIV. They advise that PEP emergency starter packs should contain two nucleoside reverse transcriptase inhibitors (NsRTIs) (tenofovir and emtricitabine) and a boosted HIV-protease inhibitor (lopinavir-ritonavir).

Guidelines in the USA[4] recommend selection of PEP regimens based on the level of risk of transmission presented by the exposure and other considerations such as possible antiretroviral drug resistance in the source. Most occupational HIV exposures can be managed with a two-drug regimen, using two NsRTIs or one NsRTI and one nucleotide reverse transcriptase inhibitor (NtRTI). Although there are no definitive data to show increased efficacy of 3-drug PEP regimens over 2-drug regimens, the addition of further drugs may be considered for exposures that pose an increased risk of transmission or if antiretroviral drug resistance is likely. HIV-protease inhibitors are recommended as the preferred drug for inclusion into 3- or 4- drug regimens but the NNRTI, efavirenz, may be considered when resistance to HIV-protease inhibitors in the source person is known or suspected. Due to the higher risk for potentially serious or life-threatening adverse effects abacavir, delavirdine, nevirapine, zalcitabine, and the combination of didanosine and stavudine, are not recommended for PEP.

Measures aimed at reducing **vertical transmission** of HIV from mothers to their infants include antiretroviral therapy to the mother and baby, elective caesarean section, and avoidance of breast feeding when replacement feeding is acceptable, affordable, and safe.[5-9]

The risk of vertical transmission is directly proportional to the maternal plasma HIV viral load at the time of delivery, and very few HIV-infected children are born to mothers whose HIV viral load is undetectable. The benefit of elective caesarean section is therefore most profound in women with detectable or high HIV viral loads. In contrast, zidovudine monotherapy given during pregnancy and labour, and to the infant postpartum, reduces the rate of vertical transmission by about 70%, irrespective of maternal viral load or CD4+ count.[10,11] However, zidovudine monotherapy is suboptimal for mothers with high viral loads, in whom combination antiretroviral therapy should be used to prevent vertical transmission.

In resource-limited settings, infants born to HIV-infected mothers who are not breast fed are at very high risk for mortality or morbidity. This risk can exceed that associated with HIV-infection and WHO therefore recommends exclusive breast feeding for infants born to HIV-infected women for the first 6 months of life if replacement feeding is not acceptable, feasible, affordable, sustainable and safe.[12] However, breast feeding continues to expose the infant to the risk of HIV infection and studies are ongoing to determine if extending the duration of antiretroviral prophylaxis will reduce HIV transmission via breast feeding. Extended prophylaxis for the first 14 weeks of life with nevirapine or with nevirapine plus zidovudine significantly reduced postnatal HIV infection in 9-month-old infants,[13] but extended treatment for the first 6 weeks of life with nevirapine did not reduce the risk of HIV transmission at 6 months of age.[14] The use of nevirapine in this manner is controversial because it rapidly induces resistance to NNRTIs.[15] Extended prophylactic treatment of infants with lamivudine, for a maximum of 6 months during breastfeeding, was found to be effective in reducing HIV transmission.[16] Another approach being investigated to prevent postnatal HIV transmission is to continue HAART treatment during breastfeeding in those HIV-infected mothers who received HAART during pregnancy solely for prophylaxis of perinatal HIV transmission.[17]

Guidelines for the management of HIV infection in pregnant women and for the prevention of transmission of HIV from mother to child have been developed for the USA[7] and the UK.[9] The *US guidelines*[7] recommend that zidovudine-based therapy is of proven benefit in preventing perinatal HIV transmission, but three-drug combination drug regimens should be considered the standard of care for both treatment of HIV infection in pregnant women and prevention of perinatal HIV transmission. Treatment to prevent the latter should be offered to all women, regardless of CD4 count and viral load:

- women who are taking HAART and become pregnant should continue with their regimen, although regimens with potentially teratogenic drugs such as efavirenz should be substituted in the first trimester, as should combinations with known adverse potential for the mother, such as stavudine/didanosine. If an HIV-protease inhibitor is required, ritonavir-boosted lopinavir is the drug of choice; alternatives include ritonavir-boosted atazanavir, indinavir, or saquinavir. Treatment should be continued both during labour (with zidovudine given intravenously and other antiretroviral drugs given orally), and postpartum
- women who have not had antiretroviral treatment and have indications for therapy should also begin HAART, subject to the same precautions as above; those who do not require HAART for their own health should be offered it for prevention of perinatal transmission, but treatment may be delayed until after the first trimester, and should be stopped postpartum unless indications for continuing it develop. If the regimen includes a long half-life NNRTI, consideration should be given to continuing NRTIs for at least 7 days after stopping the former
- women who have previously had antiretrovirals should be offered an HAART regimen based on resistance testing; use of zidovudine as a component of the regimen is recommended when feasible. Need for continuing therapy should be evaluated postpartum
- in all cases above, the *infant* should be treated with zidovudine intravenously or orally for 6 weeks, starting 6 to 12 hours after birth; the course may be reduced to 4 weeks where adherence or toxicity is a problem
- in women who have had no antiretroviral therapy before labour, treatment should be offered with:
  - *mother*: continuous infusion of zidovudine during labour; *infant*: zidovudine for 6 weeks started within 6 to 12 hours of birth
  - *or*
  - *mother*: continuous infusion of zidovudine during labour, plus a single dose of nevirapine at onset; consideration should be given to adding lamivudine during labour and zidovudine and lamivudine for 7 days postpartum, to reduce development of nevirapine resistance; *infant*: single oral dose of nevirapine at 2 to 3 days after birth, plus zidovudine for 6 weeks
- if the mother has no antiretroviral therapy either before or during labour, the infant should still be given zidovudine for 6 weeks, started as soon as possible after birth. The use of other drugs for prophylaxis in infants requires specialist consultation

While similar to those of the USA, the *UK guidelines*[9] recommend that zidovudine monotherapy combined with elective caesarean section may still be an option for pregnant women in whom HAART is contra-indicated and whose HIV viral load is less than 10 000 copies/mL, or for women not wishing to take HAART during pregnancy. Infants born to HIV-infected mothers should be given zidovudine for 4 weeks after birth. Alternative antiretroviral

therapy may be given to infants whose mothers did not take zidovudine in their treatment regimen and triple therapy may be considered for infants whose mothers had no antiretroviral therapy or whose mothers are infected with drug-resistant HIV.

WHO has published guidelines on the use of antiretrovirals in pregnancy and for preventing HIV transmission to infants in *resource-limited settings*[4] and has updated them in line with available evidence.[5]

- In countries where HAART is available, women with a CD4+ T lymphocyte count below 350 cells/microlitre and those with a CD4+ T lymphocyte count greater than 350 cells/microlitre who have other indications for antiretroviral treatment should start HAART during their pregnancy. The preferred regimens are zidovudine plus lamivudine and either nevirapine or efavirenz. Alternative recommended regimens include tenofovir, plus lamivudine or emtricitabine, and nevirapine or efavirenz.[5] However, efavirenz-based regimens should not be started during the first trimester of pregnancy.
  Women already taking antiretrovirals should continue their therapy; but consideration should be given to switching those who are in the first trimester of pregnancy and taking efavirenz to a nevirapine-containing regimen
  Non-breast fed infants born to these mothers should be given zidovudine or nevirapine from birth until 6 weeks of age; breast-fed infants should be given nevirapine from birth until 6 weeks of age[5]
- Women in whom maternal HAART is not indicated, or those living in countries where HAART is not available, should be given short-course zidovudine starting at 14 weeks of pregnancy or as soon as feasible thereafter and continued into labour. A single dose of nevirapine should be given at the onset of labour to the mother. Zidovudine and lamivudine are given during labour and delivery and then for 7 days postpartum to reduce the emergence of nevirapine resistance. The single dose of nevirapine, and the zidovudine plus lamivudine given intra- and postpartum, can be left out if the mother has received more than 4 weeks of zidovudine during pregnancy
  Non-breast fed infants born to these mothers should be given zidovudine or nevirapine from birth until 6 weeks of age; breast-fed infants should be given nevirapine from birth until 1 week after exposure to breast milk is stopped[5]
- Another option for HIV-infected women being treated to prevent perinatal transmission to the infant, but not in need of therapy for their own health is triple antiretroviral therapy starting from as early as 14 weeks of gestation until one week after all exposure to breast milk has ended. The recommended regimens include zidovudine, lamivudine plus either ritonavir-boosted lopinavir, abacavir or efavirenz, *or* alternatively tenofovir, emtricitabine or lamivudine, plus efavirenz
  Non-breast fed infants born to these mothers should be given zidovudine or nevirapine from birth until 6 weeks of age; breast-fed infants should be given nevirapine from birth until 6 weeks of age.[5]

Other measures necessary to minimise the transmission of infection include the rigorous selection of blood donors, microbiological screening of blood, and, where possible, heat treatment of blood products. Maternal vitamin A deficiency has been identified as a risk factor for vertical transmission in Africa (see p. 2100.2). Nutritional intervention and vaginal cleansing during labour could reduce vertical transmission in regions where zidovudine therapy is not readily available.

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Infections in immunocompromised patients

Most viral infections present in a more severe form in immunocompromised patients than in immunocompetent patients. Among the viral infections that may be a particular problem in immunocompromised patients are hepatitis, herpesvirus infections (including CMV and Epstein-Barr virus infections), measles, and RSV infections. For further information and treatment of these infections, see under the individual diseases. For secondary infections occurring in HIV-infected patients, see p. 958.3.

Persistent infection with human **parvovirus B19** can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients; treatment with immunoglobulin has been reported to be successful.

Infection with a polyomavirus (JC virus)[1,2] can cause **progressive multifocal leukoencephalopathy**. Although no treatment has been consistently successful,[1] prolonged survival has been reported in patients receiving interferon alfa[3] and in those receiving HAART.[4–6] Cidofovir may be of benefit in patients unresponsive to HAART.[7,8] Rarely, JC virus, and much more commonly a related polyomavirus, BK virus,[9] have been associated with **polyomavirus-associated nephropathy** (PVAN) in renal transplant patients, a condition associated with poor prognosis for graft survival. BK virus is also associated with haemorrhagic cystitis after stem-cell transplantation.[10] Cidofovir[11] has been investigated for management of BK virus infections.

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Influenza

Influenza is an acute respiratory-tract infection caused by RNA viruses of the family Orthomyxoviridae. Three types of influenza virus, A, B, and C, have been classified. Type A causes most infections in man; type B causes a similar though possibly milder infection than type A; type C generally only causes mild infection. Epidemic influenza is usually caused by the type A influenza virus. Outbreaks of influenza due to the type A virus occur in most years while those due to the type B virus tend to occur at intervals of several years. Influenza viruses are antigenically labile with the principal surface antigens, haemagglutinin and neuraminidase, undergoing frequent changes. Major changes (antigenic shifts) in these surface antigens occur periodically and are responsible for the emergence of the subtypes of virus which may cause pandemic influenza; minor changes (antigenic drift) occur more frequently and are responsible for the annual epidemic outbreaks of influenza.

Influenza is transmitted from person to person in respiratory droplets with an incubation period of 1 to 2 days. Infection with influenza A or B virus usually lasts for about 1 to 2 weeks and is characterised by sudden onset of fever, chills, headache, malaise, myalgia, dry cough, nasal obstruction, and a dry or sore throat. Infections are usually acute but self-limiting and persons with pre-existing immunity, or those who have received influenza vaccine, have less severe symptoms. Complications that may occur in the course of infection include primary viral pneumonia, secondary bacterial pneumonia, croup, exacerbation of asthma or chronic bronchitis, myositis, Reye's syndrome, and the toxic shock syndrome. Patients at high risk of complications include the elderly, children less than 5 years of age and particularly those less than 2 years of age, persons 18 years of age or less who are receiving long-term aspirin therapy, those who are morbidly obese, women who are pregnant or up to 2 weeks postpartum, persons with haemoglobinopathies, immunocompromised individuals, and those with heart disease, chronic chest disease, metabolic disorders, chronic renal disease, chronic liver disease, and certain neurological disorders.

Since 1997, infection of humans with avian influenza virus H5N1 (so-called 'bird flu') has been reported, initially in Hong Kong. Avian influenza may cause severe illness and is associated with high mortality. Since then cases have also been reported in other Asian countries and in the near East. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic.[1,2] In April 2009 an influenza outbreak in humans, first detected in Mexico, and termed pandemic (H1N1) 2009 influenza (previously referred to as novel influenza A (H1N1) and also known as swine flu), was caused by a new strain of influenza A virus, subtype H1N1. Infections had been reported worldwide and on 11th June 2009 WHO declared a worldwide pandemic. Because there was little or no pre-existing immunity to the virus the impact of the infection has occurred in a wider age range than seasonal influenza (particularly children and young adults). Additionally, it can infect the lower respiratory tract and cause rapidly progressive pneumonia especially in children and young to middle-aged adults. Although most patients have a milder disease and recover without antiviral treatment or medical care, severe complications including fatal outcomes have occurred. In those who required hospitalisation, more than half had underlying health conditions or weak immune systems. However, about a third of those with very severe illness admitted to an intensive care unit were previously healthy. By August 2010 epidemiological data indicated that the behaviour of the virus and its patterns of transmission were transitioning towards that of seasonal influenza and WHO announced that the (H1N1) 2009 influenza pandemic was over. However, sporadic and localised outbreaks may continue to cause serious disease in high-risk groups in the post-pandemic period.[3] WHO has developed detailed guidelines for the pharmacological management of avian influenza[4,5] and pandemic (H1N1) 2009 influenza[6,7] in humans. Similar guidelines for the management of an influenza pandemic have been developed in many countries.[8–10]

The most effective means of **preventing** influenza is to provide seasonal vaccination with *influenza vaccine* adjusted to take account of current antigenic drifts and shifts and to provide protection against both influenza A and B. WHO[11] recommends that elderly individuals and persons of any age who are considered to be at high risk of influenza-related complications should be vaccinated. Similar recommendations have been made in the UK[12] and USA.[13–15]

In healthy adults living in industrialised countries, protective efficacy of influenza vaccine is about 70 to 90%, and vaccination of the elderly living in the community reduces the number of hospitalisations by 25 to 39% and death by 39 to 75%.[11] Vaccines have been developed against 2009 pandemic (H1N1) influenza and avian influenza. For further information see under Influenza Vaccines, p. 2393.3.

Four antiviral drugs are available for the prevention of influenza: the M2 ion channel inhibitors, amantadine and rimantadine (adamantanes), and the neuraminidase inhibitors, oseltamivir and zanamivir. Antivirals appear to act independently of vaccination and provide additional barriers to the virus, but should not be used as a substitute for vaccination. They may be considered for postexposure prophylaxis, for seasonal prophylaxis in unvaccinated individuals at high risk, for persons who take care of those at

high risk, and in vaccinated individuals if an influenza outbreak occurs less than 2 weeks after vaccination with an inactivated vaccine, or if circulating influenza strains are thought to be different to the vaccine strain. Prophylaxis with antivirals may also be considered in vaccinated immunocompromised individuals whose antibody response to the vaccine is likely to be incomplete.[16,17] Postexposure prophylaxis should be started within 48 hours of the most recent exposure and is given for no more than 10 days.[18] Preexposure prophylaxis should be given for the duration of time when exposure might occur.[18]

Amantadine and *rimantadine*, when started before exposure and continued throughout the period of exposure, are effective in preventing influenza A in 60 to 90% of patients. They are ineffective against influenza B and therefore cannot be considered as a substitute for vaccination unless the vaccine is contra-indicated.[19] Additional problems with these drugs are the rapid development of viral resistance and subsequent spread of resistant virus to close contacts and the potential to cause serious CNS adverse effects. All strains of influenza anticipated to circulate during the 2011-2012 winter influenza seasons, including pandemic (H1N1) 2009 influenza strains, are resistant to adamantanes.[13]

A systematic review[20] of clinical studies in healthy adults and children indicated that both the neuraminidase inhibitors, *oseltamivir* and *zanamivir*, were effective in preventing and treating the symptoms of influenza A and B but they do not prevent pneumonia or stop influenza viruses from spreading from person-to-person.

In the USA, all 4 antiviral drugs are licensed for postexposure prophylaxis of influenza but only oseltamivir and zanamivir are recommended by the Advisory Committee on Immunization Practices[18] and the American Academy of Pediatrics.[13] In the UK, amantadine, zanamivir, and oseltamivir are licensed for prophylaxis, but only oseltamivir and zanamivir were recommended by NICE[21] for postexposure prophylaxis in those at high risk of complications of influenza. Recommendations did not favour use for seasonal prophylaxis of influenza.

For most people **treatment** of influenza is largely symptomatic and supportive. However, antivirals may be used for the treatment of vaccinated or unvaccinated individuals who develop symptoms. *Amantadine* and *rimantadine* have been shown to reduce the duration of uncomplicated influenza A infection when given within 48 hours of the onset of symptoms. These drugs may be considered for patients at high risk of complications. Treatment failures may be due to the rapid emergence of drug resistance.[19,22] They are not effective against influenza B,[16] seasonal influenza A (H3N2), or the pandemic (H1N1) 2009 strain.[6] *Oseltamivir* and *zanamivir* given within 48 hours of the onset of symptoms are active against both influenza A and B viruses and reduce the duration of uncomplicated influenza by about 1 day in healthy adults and adolescents. Data are limited and inconclusive for all 4 drugs in terms of efficacy when given to individuals at high risk of complications of influenza. Neuraminidase inhibitors have several advantages compared with amantadine, including reduced viral resistance, additional efficacy against influenza B, fewer adverse effects (including CNS effects), and reduction in clinical symptoms. Viral strains resistant to amantadine and rimantadine generally remain susceptible to neuraminidase inhibitors.[20,22]

In the UK, oseltamivir and zanamivir are recommended[23] for the treatment of those at risk of complications of influenza who can start treatment within 48 hours (or within 36 hours for zanamivir treatment in children) of the onset of symptoms. In the UK NICE does not recommend the use of amantadine for the treatment of influenza. In the USA, the Advisory Committee on Immunization Practices[18] and the American Academy of Pediatrics[13] recommend oseltamivir or zanamivir for treatment of acute illness caused by influenza A and B. Treatment is given for 5 days, although longer treatment regimens might be needed in hospitalised and immunosuppressed patients. Treatment should be started as soon as possible (ideally within 48 hours of illness onset), but treatment may still be of benefit in patients with severe or progressive illness and in hospitalised patients if started after 48 hours.[18] Neuraminidase inhibitors have also been effective against some strains of avian influenza in *animal* studies and may be considered for both prophylaxis and treatment of suspected infections,[2] although WHO recommends oseltamivir as the treatment of choice.[5]

Peramivir is a neuraminidase inhibitor that is given intravenously; although it has not yet been approved for marketing in the USA, the FDA has authorised its emergency use to treat certain adult and paediatric patients with suspected or laboratory-confirmed pandemic (H1N1) 2009 influenza, or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology. Laninamivir octanoate has been licensed for use in Japan. It is a long-acting neuraminidase inhibitor given as a single oral inhalation for the treatment of influenza. Intravenous formulations of oseltamivir and zanamivir are under investigation and available on a compassionate use basis in some countries for the treatment of influenza.[6,16]

Pregnant women with confirmed or suspected influenza should be given antiviral treatment as they are known to be at higher risk for complications from infection.[6,18] Oseltamivir is preferred for treatment of pregnant women although zanamivir might be preferred by some providers because of its limited systemic absorption.[18]

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Measles

Measles[1] is an acute viral illness caused by an RNA virus of the Morbillivirus genus and of the family Paramyxoviridae. It is a highly contagious disease spread by airborne droplets or direct contact with respiratory secretions of infected persons. Infection confers lifelong immunity.

The incubation period for measles is about 8 to 12 days followed by a prodromal phase lasting several days. This phase is usually characterised by malaise, fever, conjunctivitis, cough, rhinitis, congestion, and later Koplik's spots on the buccal mucosa. An erythematous, maculopapular rash appears towards the end of the prodromal phase, starting on the face and spreading over the trunk and limbs. Measles is generally benign and uncomplicated and recovery usually takes place during the week after the rash's appearance. However, severe disease and complications may develop and are more common in adults and in children who are undernourished or immunocompromised. Most complications occur when the measles virus further suppresses host immune responses, resulting in a reactivation of latent infections or superinfection by bacteria. Respiratory complications include giant cell pneumonia, bronchopneumonia, and laryngotracheobronchitis, while neurological complications include febrile seizures, acute encephalitis, progressive subacute encephalitis, and the more slowly progressive subacute sclerosing panencephalitis (SSPE) which may develop several years after the original measles infection. Other complications include diarrhoea, otitis media, thrombocytopenia with purpura and bleeding, hepatitis, myocarditis, pericarditis, and severe keratitis that may progress to blindness.

Measles can be **prevented** by active immunisation with measles vaccine, and measles immunoglobulins may be used for passive immunisation against measles. Normal immunoglobulins may be used to prevent, or possibly modify, an attack of measles in those at risk of developing severe or fatal disease such as immunocompromised patients.

Measles usually requires only symptomatic and supportive **treatment** such as antipyretics and fluid replacement. *Vitamin A* treatment for children with measles in developing countries has been associated with a significant reduction in mortality (see p. 2100.3). A systematic review of randomised studies concluded that a dose of 200 000 units of vitamin A given on 2 consecutive days reduced mortality in children under 2 years with measles.[2] WHO recommends that supplementary vitamin A be given to all children with measles in developing countries in order to prevent keratitis and blindness. A recent review has suggested that prophylactic antibacterials may be of benefit in preventing complications such as pneumonia, purulent otitis media, and tonsillitis in children with measles but of no benefit for conjunctivitis or gastroenteritis;[3] evidence from earlier reviews did not support such use.[4,5] However, prompt antibacterial therapy should be given to those patients who develop keratitis, otitis media, or pneumonia. There appears to be no good evidence for the use of antivirals, although there are case reports of ribavirin being used to treat severely affected and immunocompromised adults with acute measles[6] or patients with subacute sclerosing panencephalitis (intravenous ribavirin plus intrathecal high-dose interferon alfa[7] or intraventricular ribavirin[8]). No controlled studies have been conducted and the use of ribavirin should be considered experimental.

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Respiratory syncytial virus infection

Respiratory syncytial virus (RSV) is an RNA virus of the family Paramyxoviridae and occurs worldwide. RSV is a prominent cause of respiratory infections in infants and young children and is generally confined to the respiratory tract. However, disease may occur at any age, and it has been recognised as a cause of morbidity and mortality among the elderly,[1] as well as among children and adults with compromised cardiac, respiratory, or immune systems. RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated environmental surfaces. RSV infection is highly contagious and may result in extensive nosocomial transmission. RSV outbreaks tend to occur annually, usually from late autumn through to early spring.

Primary infection in infants and young children is characterised by fever, cough, runny or congested nose, vomiting, and sometimes wheezing. During the primary infection up to 50% of infants develop lower respiratory-tract disease, most commonly bronchiolitis and pneumonia, and about 1 to 2% of these infants may require hospitalisation. Most infants needing hospitalisation are less than 6 months old or at risk of severe infection, for example because of a history of prematurity, or pre-existing cardiac or respiratory diseases or immunodeficiency. Otitis media and persistent wheezing are common complications of RSV infection in infants and young children. RSV

infection may trigger acute respiratory distress syndrome and exacerbate pre-existing, underlying cardiac, renal (nephrotic syndrome), or lung (cystic fibrosis) disease. Acquired immunity does not prevent re-infection, although subsequent infections are typically milder.

The management of mild RSV infection in infants and children[2-7] consists of supportive care such as fever control and adequate hydration. Children with more severe lower respiratory-tract disease may require hospitalisation for supplementary oxygen. Measures to limit the spread of infection in hospitals and institutions are important. Pharmacological therapies are of limited benefit. $Beta_2$-agonist *bronchodilators* are often used in the management of bronchiolitis even though systematic reviews and meta-analyses of studies have indicated only modest short-term benefit of clinical symptoms and no reduction in hospital admission rates, length of hospital stay, or improvement in oxygen saturation.[2,8] A review[9] of the use of the anticholinergic bronchodilator ipratropium bromide reported no proven efficacy. An evaluation of clinical studies[2] using nebulised or intravenous adrenaline to treat RSV infection has reported clinical benefit in some infants, as well as a reduction in hospital admission or stay. However, a systematic review[10] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients. If a bronchodilator or inhaled adrenaline is tried, it should be stopped if no response is evident after 1 or 2 treatments.[2,4]

Nebulised hypertonic *saline* is thought to increase clearance of mucus and a systematic review[11] of 4 randomised studies involving 254 infants up to 24 months of age suggested that nebulised 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score of acute viral bronchiolitis.

Systemic *corticosteroids* are also widely used despite a lack of documented clear benefit. A systematic review[12] found little benefit in terms of length of hospital stay or admission rate and no evidence of improvement in clinical scores, respiratory rate, or oxygen saturation when compared with placebo. Although a later study[13] found that a 3-day course of oral prednisolone given to children aged 6 to 35 months with respiratory distress reduced disease severity, length of hospital stay, and the duration of symptoms another[14] showed that a single oral dose of dexamethasone was of no benefit in infants with moderate to severe bronchiolitis. A double-blind, placebo-controlled study[15] in 800 infants with bronchiolitis suggested that treatment with oral dexamethasone plus nebulised epinephrine might significantly reduce hospital admissions. The routine use of systemic corticosteroids is not recommended by expert groups.[4,5] *Inhaled corticosteroids* given during the initial acute phase of bronchiolitis did not prevent post-bronchiolitic wheezing.[16]

Ribavirin is the only antiviral drug that has been licensed for the treatment of infants and children with severe RSV bronchiolitis (and it is only available in some countries). Although some studies with aerosolised ribavirin have shown some clinical benefit in infants with lower respiratory-tract RSV infection, days of hospitalisation and short-term outcomes have not been affected.[2] Due to the small number of patients enrolled in these studies, evaluation of the effects has been difficult. Also, there are some difficulties in giving the drug, and concerns about occupational health and safety, and the high cost. Routine use is not recommended;[4,5] but it may be used for selected infants and children at risk of severe disease and complications. If used, ribavirin should be started early in the course of the disease.[2-4]

Antibacterials, although often used in the management of bronchiolitis, are not routinely recommended.[4,5] The results from three small studies[17-19] suggest that *surfactant* may reduce duration of ventilation and length of intensive care stay.

Prevention of RSV infection involves good infection control practices and use of *RSV immunoglobulin* and a human monoclonal antibody to RSV, *palivizumab*. Both RSV immunoglobulin and palivizumab can be given during an RSV outbreak to prevent serious complications of infection in infants and children considered at high risk. The efficacy of RSV immunoglobulin[20] and palivizumab[21] were tested in randomised, placebo-controlled clinical studies involving high-risk infants and children (history of prematurity or with bronchopulmonary dysplasia). A 41% overall reduction in hospital admissions was reported in those given RSV immunoglobulin prophylaxis. Prophylaxis with palivizumab resulted in a 55% overall reduction in hospitalisation; reduction rates were 39% and 78% in those with and without bronchopulmonary dysplasia respectively. Respiratory severity scores, hospital days, days of oxygen requirement, and the rate of intensive care admission were also significantly lower in the palivizumab group than for the placebo group. Prophylaxis with palivizumab was also found to reduce post-bronchiolitic wheezing in premature infants.[22] It is recommended by some expert groups for prophylaxis in infants and children at high risk of severe RSV infections.[4,5,23] Vaccines to prevent RSV infection are currently under development.

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SARS

Severe acute respiratory syndrome (SARS)[1,2] is a respiratory illness caused by a coronavirus (SARS-CoV). SARS presents mainly in previously healthy adults although there have been some cases reported in children. SARS-CoV is transmitted by contact or droplets and transmission mainly occurs during the second week of illness. The incubation period for SARS is usually 2 to 10 days but may be as long as 16 days. The disease manifests initially as flu-like prodromal symptoms, usually characterised by fever, malaise, myalgia, headache, and rigors. Cough (initially dry), dyspnoea, and diarrhoea may be present in the first week but are more commonly present in the second week of illness. Severe cases develop rapidly progressive respiratory distress and hypoxia and up to about 20% of patients may require intubation or mechanical ventilation. About 20% of patients develop large volume, watery diarrhoea. The overall fatality rate during the 2002–2003 SARS outbreak was about 9.5%.

There is currently no consensus on the optimal treatment for SARS and treatment recommendations are based on the experience gained during the 2002–2003 SARS outbreak. Guidelines for the **surveillance and management** of SARS have been developed by WHO.[3] In the UK guidelines[4] have been issued for the hospital management of adults with SARS, and others have also been developed by clinicians involved in the SARS outbreak in Hong Kong.[5] Because SARS is indistinguishable from pneumonia caused by viral and bacterial pathogens, empirical antibacterial treatment in accordance with local guidelines for severe community-acquired pneumonia (p. 200.1) is recommended. Fluids and oxygen therapy should be given as required. Other treatments tried have included corticosteroids, ribavirin, interferons, normal immunoglobulins, and the co-formulated HIV-protease inhibitor ritonavir-boosted lopinavir. Corticosteroids, usually with ribavirin, were widely used and the timely use of high-dose corticosteroids may decrease fever, improve radiographic appearances, and reduce oxygen requirements.[6-8] There is, however, concern that high-dose and long-term use of corticosteroids may suppress the patient's immune system resulting in increased viral replication and possible bacterial or fungal super-infection. The UK guidelines recommend that their use be considered in moderate doses in severely ill patients with increased oxygen requirements.[4] Additionally there is no convincing clinical evidence that the use of ribavirin alters clinical outcome and the UK guidelines state that its routine use is not recommended.[4] Although interferon beta shows greater *in-vitro* antiviral activity against SARS-CoV, most experience during the 2002–2003 outbreak was with interferon alfa with or without normal immunoglobulins.[6] An open study[9] using interferon-alfacon-1 and high dose pulse methylprednisolone reported more rapid improvement in radiographic appearance and oxygenation than corticosteroids alone. Better clinical improvement was reported in patients treated with daily interferon alfa plus high-dose corticosteroids than in those given interferon plus low-dose or limited corticosteroids.[8] The UK guidelines state that no recommendation can be given regarding the use of interferons.[4] Although normal immunoglobulins have been used in SARS their efficacy cannot be established as they were usually given with other therapies.[6] A preliminary open study[10] with ritonavir-boosted lopinavir in 41 patients with probable SARS and receiving the local standard treatment of ribavirin and corticosteroids, reported an improved outcome at 21 days and reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections. Chloroquine and niclosamide have both been reported to have some activity against the virus *in vitro*,[11] but have not been tried clinically. Newer antivirals specific for coronaviruses[12,13] and vaccines against SARS-CoV[14] have been investigated.

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Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Anogenital warts are known as condylomata acuminata. Treatment generally relies on some form of local tissue destruction (see p. 1689.1). Interferons have also been used (see p. 992.1).

Abacavir *(BAN, rINN)*

Abacavirum; Abakaviiri; Abakavir; Abakawir; Абакавир.

{(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl}methanol.

$C_{14}H_{18}N_6O$=286.3

CAS — 136470-78-5.

ATC — J05AF06.

ATC Vet — QJ05AF06.

UNII — WR2TIP26VS.

NOTE. The code 1592U89 has been applied to abacavir but is more properly reserved for abacavir sulfate.

Abacavir Succinate *(BANM, USAN, rINNM)*

Abacavir, Succinate d'; Abacavir, succinato de; Abacaviri Succinas; Succinato de abacavir; Абакавира Сукцинат.

$C_{14}H_{18}N_6O.C_4H_6O_4$=404.4

CAS — 168146-84-7.

ATC — J05AF06.

ATC Vet — QJ05AF06.

UNII — 40FH6D8CHK.

NOTE. The code 1592U89 has been applied to abacavir succinate but is more properly reserved for abacavir sulfate.

Abacavir Sulfate *(BANM, USAN, rINNM)*

1592U89; Abacavir, Sulfate d'; Abacavir, sulfato de; Abacavir Sulphate; Abacaviri Sulfas; Sulfato de abacavir; Абакавира Сульфат.

$(C_{14}H_{18}N_6O)_2.H_2SO_4$=670.8

CAS — 188062-50-2.

ATC — J05AF06.

ATC Vet — QJ05AF06.

UNII — J220T4J9Q2.

NOTE. The code 1592U89 and its abbreviated form, 1592, have also been applied to abacavir and abacavir succinate.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Abacavir Sulfate). A white or almost white powder. Soluble in water; practically insoluble in alcohol and in dichloromethane.

USP 36: (Abacavir Sulfate). A white to off-white powder. Soluble in water, in absolute alcohol, in methyl alcohol, and in ethyl acetate.

Uses and Administration

Abacavir is a nucleoside reverse transcriptase inhibitor with antiretroviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when abacavir is used alone, and it is therefore used with other antiretrovirals.

Abacavir is given orally as the sulfate but doses are expressed in terms of the base; 1.17 g of abacavir sulfate is equivalent to about 1 g of abacavir. The adult dose is 300 mg twice daily or 600 mg once daily. For details of doses in children, see below. Doses should be reduced in patients with hepatic impairment (see below).

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing abacavir in combination with lamivudine and with lamivudine and zidovudine are available in some countries.

Reviews.

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2. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; 65: 285–302.
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Administration in children. For the treatment of HIV infection in children 3 months of age and older, abacavir may be given orally as a tablet or solution with other antiretroviral drugs. Doses are based on body-weight:

- 14 to 21 kg: 150 mg (half a tablet) twice daily
- 22 to 29 kg: 150 mg (half a tablet) in the morning and 300 mg (1 tablet) in the evening
- 30 kg or more: 300 mg (1 tablet) twice daily

or

- the solution may be given in a dose of 8 mg/kg twice daily to a maximum dose of 300 mg twice daily

Administration in hepatic impairment. Abacavir should not be used in patients with moderate to severe hepatic impairment, although reduced oral doses of 200 mg twice daily may be given to patients with mild impairment (Child-Pugh score 5 to 6).

Adverse Effects

The most significant adverse effects associated with antiretroviral regimens containing abacavir are severe and sometimes fatal hypersensitivity reactions that may occur especially (but not exclusively) during the first 6 weeks of treatment, or during intermittent therapy (see also below). Symptoms of hypersensitivity often include fever, rash, cough, dyspnoea, lethargy, malaise, headache, myalgia, and gastrointestinal disturbances, particularly nausea and vomiting, diarrhoea, and abdominal pain. Anaphylaxis has occurred. Caution is needed as hypersensitivity may be misdiagnosed as influenza, respiratory disease, or gastroenteritis. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Other adverse effects associated with abacavir include pancreatitis and raised liver enzyme values. Lactic acidosis, sometimes fatal and usually associated with severe hepatomegaly and steatosis, has been reported in patients receiving NRTIs, but is thought to be less likely with abacavir than with others such as didanosine, stavudine, or zidovudine.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including abacavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, although the risk associated with abacavir use is relatively low. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactatemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the heart. For the possible risk of myocardial infarction in patients taking abacavir, see Effects on the Heart under Adverse Effects of Zidovudine, p. 1025.2.

Effects on the skin. Stevens-Johnson syndrome occurring in a patient receiving antiretroviral therapy with abacavir, lamivudine, and zidovudine was probably associated with abacavir.[1] Resolution occurred upon stopping antiretroviral therapy and the condition did not recur upon rechallenge with an alternative regimen also containing lamivudine and zidovudine.

1. Bossi P, *et al.* Stevens-Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; 35: 902.

Hypersensitivity. Hypersensitivity reactions occur in about 5% of patients starting treatment with abacavir,[1,2] generally within the first 6 weeks.[2] Symptoms typically occur suddenly and worsen with each consecutive abacavir dose.[2] Re-starting abacavir in a patient with a history of hypersensitivity syndrome can cause severe, rapidly progressive, and potentially fatal reactions.

Risk of developing hypersensitivity to abacavir appears to be related to race, and history of antiretroviral use; it is thought to be lower in antiretroviral-experienced patients, and those of African descent.[1,2] Carriage of the major histocompatibility complex class I allele HLA-B(*)5701 has been found to be the most significant predictor of whether or not a patient will be hypersensitive to abacavir.[2] The multicentre PREDICT-1 study[3] confirmed that prospective HLA-B(*)5701 screening was effective in reducing the incidence of abacavir hypersensitivity reaction.

1. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002; 34: 1137–42.
2. Hughes CA, *et al.* Abacavir hypersensitivity reaction: an update. *Ann Pharmacother* 2008; 42: 387–96.
3. Mallal S, *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; 358: 568–79.

Precautions

Patients considered to be at increased risk for an abacavir hypersensitivity reaction are those that carry the human leucocyte antigen HLA-B(*)5701 allele; screening patients for this allele before starting treatment with abacavir has been shown to reduce the risk of hypersensitivity reactions. Routine screening of all patients before starting treatment with an abacavir-containing product is therefore recommended including in those who tolerated previous treatment with abacavir but have unknown HLA-B(*)5701 status. Abacavir should be stopped immediately if symptoms associated with hypersensitivity occur and should *never be restarted* in patients who have stopped therapy due to a hypersensitivity reaction. Patients should be closely monitored for signs of hypersensitivity during the first 2 months of treatment, although such reactions can occur at any time. Patients restarting therapy after an interruption are at particular risk even if they have not previously had symptoms of hypersensitivity. Since intermittent therapy may increase the risk of reactions patients should be advised of the importance of regular dosing.

Although the suggestion in some studies that use of abacavir in the previous 6 months was associated with an increased risk of myocardial infarction does not seem to have been borne out (see Effects on the Heart under Adverse Effects of Zidovudine, p. 1025.2), underlying risk of cardiovascular disease should be considered and efforts made to minimise risk factors.

Abacavir should not be used in patients with moderate to severe hepatic impairment, and should be used with caution and reduced doses in those with lesser degrees of impairment and those with risk factors for liver disease. Treatment should be stopped if liver function deteriorates rapidly or if hepatomegaly or unexplained metabolic acidosis develop.

Abacavir should be avoided in patients with end-stage renal disease.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies abacavir as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Use of alcohol with abacavir may result in decreased elimination of abacavir and consequent increases in exposure. Abacavir increases the systemic clearance of oral methadone and patients should be monitored for signs of withdrawal symptoms. The dose of methadone may need to be increased in some patients.

Alcohol. References.

1. McDowell JA, *et al.* Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000; 44: 1686–90.

Antiviral Action

Abacavir is converted intracellularly in stages to its active form carbovir triphosphate. This halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

References.

1. Faletto MB, *et al.* Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. *Antimicrob Agents Chemother* 1997; 41: 1099–1107.

Pharmacokinetics

Abacavir is rapidly absorbed after oral doses with a bioavailability of about 80%. Absorption is delayed slightly by food but the extent is unaffected. Abacavir crosses the blood-brain barrier. It is about 50% bound to plasma proteins. The elimination half-life is about 1.5 hours after a single dose. Abacavir undergoes intracellular metabolism to the active antiviral metabolite carbovir triphosphate. Elimination is via hepatic metabolism mainly by alcohol dehydrogenase and by glucuronidation and the metabolites are excreted mainly in the urine. There is no significant metabolism by hepatic cytochrome P450 isoenzymes.

References.

1. Yuen GJ, *et al.* A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; 47: 351–71.
2. Sleasman JW, *et al.* Abacavir pharmacokinetics during chronic therapy in HIV-1-infected adolescents and young adults. *Clin Pharmacol Ther* 2009; 85: 394–401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Filabac; Finecil; Panka; Plusabcir; Zepril; Ziagenavir; *Austral.*: Ziagen; *Austria*: Ziagen; *Belg.*: Ziagen; *Braz.*: Ziagenavir; *Canad.*: Ziagen; *Chile*: Ziagen; *China*: Ziagen (赛进); *Cz.*: Ziagen; *Denm.*: Ziagen; *Fin.*: Ziagen; *Fr.*: Ziagen; *Ger.*: Kivexa; Ziagen; *Gr.*: Ziagen; *Hong Kong*: Ziagen; *Hung.*: Ziagen: *India*: Abamune; Abec; *Irl.*: Ziagen; *Israel*: Ziagen; *Ital.*: Ziagen; *Mex.*: Vurtas; Ziagenavir; *Neth.*: Ziagen; *Norw.*: Ziagen; *NZ*: Ziagen; *Pol.*: Ziagen; *Port.*: Ziagen; *Rus.*: Ziagen (Зиагея); *S.Afr.*: Ziagen; *Singapore*: Ziagen; *Spain*: Ziagen; *Swed.*: Ziagen; *Switz.*: Ziagen; *Thai.*: Ziagenavir; *Turk.*: Ziagen; *UK*: Ziagen; *USA*: Ziagen; *Venez.*: Ziagen.

Multi-ingredient Preparations. *Arg.*: Kivexa; Trivicir; Trilaxis; Trivudin; Zidomuv; *Austral.*: Kivexa; Trizivir; *Austria*: Kivexa; Trizivir; *Belg.*: Kivexa; Trizivir; *Braz.*: Kivexa; *Canad.*: Kivexa; Trizivir; *Chile*: Kivexa; Trizivir; *China*: Trizivir (三协唯); *Cz.*: Kivexa; Trizivir; *Denm.*: Kivexa; Trizivir; *Fin.*: Kivexa; Trizivir; *Fr.*: Kivexa; Trizivir; *Ger.*: Trizivir; *Gr.*: Kivexa; Trizivir; *Hong Kong*: Kivexa; Trizivir; *Hung.*: Kivexa; Trizivir; *Irl.*: Kivexa; Trizivir; *Israel*: Kivexa; Trizivir; *Ital.*: Kivexa; Trizivir; *Mex.*: Kivexa; Trizivir; *Neth.*: Kivexa; Trizivir; *Norw.*: Kivexa; Trizivir; *NZ*: Kivexa; Trizivir; *Pol.*: Kivexa; Trizivir; *Port.*: Kivexa; Trizivir; *Rus.*: Kivexa (Кивекса); Trizivir (Трижавир); *S.Afr.*: Kivexa; Sonke Abacamizid; Trizivar; *Singapore*: Kivexa; Trizivir; *Spain*: Kivexa; Trizivir; *Swed.*: Kivexa; Trizivir; *Switz.*: Kivexa; Trizivir;

Thai.: Kivexa; *Turk.*: Trizivir; *UK*: Kivexa; Trizivir; *USA*: Epzicom; Trizivir; *Venez.*: Trizivir.

Pharmacopoeial Preparations
BP 2014: Abacavir Oral Solution; Abacavir Tablets;
USP 36: Abacavir Oral Solution; Abacavir Tablets.

Aciclovir *(BAN, rINN)*

Aciclóguanosina; Aciclovirum; Aciklovir; Aciklovir; Asikloviras; Acycloguanosine; Acyclovir (USAN); Acyklowir; Asikloviiri; Asiklovir; BW-248U; Ацикловир.

9-[(2-Hydroxyethoxy)methyl]guanine; 2-Amino-1,9-dihydro-9-(2-hydroxyethoxymethyl)-6*H*-purin-6-one.

$C_8H_{11}N_5O_3$=225.2

CAS — 59277-89-3.

ATC — D06BB03; J05AB01; S01AD03.

ATC Vet — QD06BB03; QJ05AB01; QS01AD03.

UNII — X4HES1O11F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Aciclovir). A white to almost white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in heptane; soluble in dilute solutions of alkali hydroxides and mineral acids.

USP 36: (Acyclovir). A white to off-white crystalline powder. Slightly soluble in water; insoluble in alcohol; soluble in dilute hydrochloric acid. Store in airtight containers. Protect from light and moisture.

Aciclovir Sodium *(BANM, rINNM)*

Aciclovir sódico; Aciclovir Sodique; Acyclovir Sodium (USAN); Natrii Aciclovirum; Натрий Ацикловир.

$C_8H_{10}N_5NaO_3$=247.2

CAS — 69657-51-8.

ATC — D06BB03; J05AB01; S01AD03.

ATC Vet — QD06BB03; QJ05AB01; QS01AD03.

UNII — 927L42J563.

Incompatibility. Aciclovir is reported to be incompatible with foscarnet.[1,2] Visual incompatibility has also been reported[3] on simulated Y-site injection between aciclovir and ciclosporin, diphenhydramine, gentamicin, granisetron, or metoclopramide.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47**: 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47**: 2075–7.
3. Canann D, *et al.* Visual compatibility of iv medications routinely used in bone marrow transplant recipients. *Am J Health-Syst Pharm* 2009; **66**: 727–9. Correction. *ibid.*; 1431.

Stability. A study[1] found that aciclovir sodium solutions prepared with sodium chloride 0.9% and with dextrose 5% were stable for 7 and 21 days respectively when stored at 23 degrees. Solutions stored at 4 degrees were found to be stable for 35 days although subsequent storage at room temperature produced irreversible precipitation. Precipitation may also occur when freshly prepared solutions are refrigerated but the precipitate redissolves at room temperature. US licensed product information recommends that diluted solutions be used within 24 hours of preparation.

1. Zhang Y, *et al.* Stability of acyclovir sodium 1, 7, and 10 mg/mL in 5% dextrose injection and 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1998; **55**: 574–7.

Uses and Administration

Aciclovir is a synthetic purine nucleoside analogue structurally related to guanine. It is used mainly for the treatment and prophylaxis of viral infections due to herpes simplex virus types 1 and 2 (p. 955.2) and varicella-zoster virus (herpes zoster and chickenpox—p. 956.2).

Herpes simplex infections, including herpes keratitis, herpes labialis, and genital herpes, respond to aciclovir by the intravenous, oral, or topical route, given as soon as possible after symptoms appear. Both initial and recurrent infections can be successfully treated. Prolonged treatment can reduce the incidence of recurrence which is particularly important in immunocompromised patients. However, when prolonged treatment is withdrawn, infections may recur. In addition, prolonged or repeated courses in severely immunocompromised patients may result in the selection of virus strains with reduced sensitivity and patients may, therefore, not respond to continued treatment.

Aciclovir also improves the healing of herpes zoster lesions and reduces acute pain when given intravenously or orally; use to prevent postherpetic neuralgia is controversial (see p. 10.3). Beneficial effects may be more marked in immunocompromised patients.

When used by ***intravenous infusion*** aciclovir is given as the sodium salt but doses are expressed in terms of the base. Aciclovir sodium 1.1 g is equivalent to about 1 g of aciclovir. Solutions for infusion are usually prepared to give a concentration of aciclovir of 25 or 50 mg/mL; this must then be further diluted to a final concentration not greater than about 5 mg/mL (0.5%) and given over 1 hour. Alternatively, a solution containing 25 mg/mL may be given by injection using a controlled-rate infusion pump, over 1 hour. In obese patients the dose should be calculated on the basis of ideal body-weight, to avoid overdosage.

For **herpes simplex infections** in the *immunocompromised*, and for severe initial *genital herpes*, or for *prophylaxis* of herpes simplex infections in *immunocompromised* patients the dose by the intravenous route is 5 mg/kg given every 8 hours, and recommended periods of treatment range from 5 to 7 days. A higher dose of 10 mg/kg every 8 hours is given in the treatment of *herpes simplex encephalitis*, and treatment is usually continued for 10 days.

For **varicella-zoster infections** in immunocompetent patients, a dose of 5 mg/kg every 8 hours may also be given. In *immunocompromised* patients the higher dose of 10 mg/kg every 8 hours should be used.

Oral doses of aciclovir also vary according to indication.

In **herpes simplex infections:**

- for treatment of *primary infections*, including genital herpes, the usual oral dose is 200 mg five times daily (usually every 4 hours while awake) for 5 to 10 days
- severely *immunocompromised* patients or those with *impaired absorption* may be given 400 mg five times daily for 5 days
- for *suppression* of recurrent herpes simplex in *immunocompetent* patients, the oral dose is 800 mg daily in two to four divided doses; dosage reduction to 400 to 600 mg daily can be tried. Higher doses of 1 g daily have also been used. Therapy should be interrupted every 6 to 12 months for reassessment of the condition
  Chronic suppressive treatment is not suitable for mild or infrequent recurrences of herpes simplex. In such cases *episodic treatment* of recurrences may be preferred; a dose of 200 mg five times daily for 5 days has been recommended, preferably begun during the prodromal period.
- for *prophylaxis* of herpes simplex in *immunocompromised* patients, the dose is 200 to 400 mg four times daily.

The usual oral dose of aciclovir for treatment of **chickenpox** is 800 mg four or five times daily for 5 to 7 days; for herpes zoster 800 mg five times daily may be given for 7 to 10 days.

For the treatment of recurrent **herpes labialis** in *immunocompetent* patients, aciclovir is available as a 50 mg mucoadhesive *buccal* tablet. One tablet should be applied as a single dose to the upper gum region within one hour of onset of prodromal symptoms. Once applied, the tablet gradually dissolves during the day; it should not be crushed, sucked, chewed, or swallowed.

In **herpes simplex infections of the skin**, including genital herpes and herpes labialis, *topical treatment* with an ointment or cream containing aciclovir 5% may be applied 5 or 6 times daily for periods of 5 to 10 days, preferably beginning in the prodromal period as soon as signs or symptoms occur. In herpes simplex **keratitis** a 3% eye ointment may be applied 5 times daily until 3 days after healing.

Doses should be reduced in *renal impairment* (see below).

For details of doses in children, see Administration in Children, below.

Reviews.
1. Wagstaff AJ, *et al.* Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47**: 153–205.
2. Leflore S, *et al.* A risk-benefit evaluation of aciclovir for the treatment and prophylaxis of herpes simplex virus infections. *Drug Safety* 2000; **23**: 131–42.
3. Nasser M, *et al.* Acyclovir for treating primary herpetic gingivostomatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 29/10/09).

Administration in children. Aciclovir is licensed for use in infants and children for the treatment of herpes simplex and varicella-zoster infections, and for the prophylaxis of herpes simplex infections in the immunocompromised. It may be given by slow intravenous infusion over 1 hour, or orally.

Recommended ***intravenous doses*** vary according to country and age of the patient. They are generally given every 8 hours.

In the *UK* the 8-hourly dose for children aged 3 months to 12 years is calculated by body-surface. The usual course of treatment is 5 to 10 days:

- herpes simplex and varicella-zoster infections in immunocompetent patients: 250 mg/m²
- varicella-zoster infection in immunocompromised children or those with herpes simplex encephalitis: 500 mg/m²

In the *USA*, the 8-hourly intravenous dose for children aged 3 months to 12 years is calculated by body-weight:

- herpes simplex infections: 10 mg/kg for 7 days
- varicella-zoster infections in immunocompromised children: 20 mg/kg for 7 days
- herpes simplex encephalitis: 20 mg/kg for 10 days

In the *UK* and the *USA* the intravenous dose for neonates and infants up to 3 months of age is calculated by body-weight; an 8-hourly intravenous dose of 10 mg/kg may be given for the treatment of herpes simplex infections. Treatment for neonatal herpes simplex usually continues for 10 days. Higher intravenous doses of 20 mg/kg every 8 hours for 14 days (21 days for CNS involvement) have been recommended by the *BNFC* for the treatment of herpes simplex infection in neonates and children up to 3 months of age. Similarly, 10 to 20 mg/kg intravenously every 8 hours is also recommended, for at least 7 days, for the treatment of herpes zoster infection in this age group.

In the *UK* the following ***oral doses*** are permitted in the treatment of herpes simplex infections, and in the prophylaxis of herpes simplex infections in the immunocompromised:

- 2 years and over: usual adult dose (see above)
- under 2 years: half usual adult dose

In the *UK* and the *USA* the oral doses for the treatment of chickenpox are:

- over 2 years: 20 mg/kg, up to a maximum of 800 mg, four times daily for 5 days

Alternatively, the following oral doses may be used:

- under 2 years: 200 mg four times daily
- 2 to 5 years: 400 mg four times daily
- 6 years and over: 800 mg four times daily

Although not a licensed indication, in the UK the *BNFC* recommends that aciclovir may also be given for postexposure attenuation of chickenpox, where varicella-zoster immunoglobulin cannot be used, in children from 1 month to 18 years of age; a dose of 10 mg/kg 4 times daily for 7 days is suggested, starting 1 week after chickenpox exposure.

Administration in renal impairment. Doses of aciclovir should be reduced in renal impairment according to creatinine clearance (CC) and licensed product information gives the following guidance:

intravenous dosage:

- CC between 25 and 50 mL/minute: the interval between infusions may be increased to 12 hours
- CC 10 to 25 mL/minute: the interval between infusions may be increased to 24 hours
- CC less than 10 mL/minute: patients on *peritoneal dialysis* should receive half the usual appropriate dose given once every 24 hours; patients on *haemodialysis* should receive half the usual dose every 24 hours plus an extra half-dose after haemodialysis

oral dosage:

- CC less than 10 mL/minute: *herpes simplex infections*: 200 mg every 12 hours; *varicella-zoster infections*: 800 mg every 12 hours
- CC between 10 and 25 mL/minute: *varicella-zoster infections*: 800 mg three times daily every 8 hours

For critically ill patients receiving renal replacement therapy, the following aciclovir doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 5 to 10 mg/kg every 24 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 5 to 10 mg/kg every 12 to 24 hours
- intermittent haemodialysis: 2.5 to 5 mg/kg every 24 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29**: 562–77.

Erythema multiforme. For patients with recurrent erythema multiforme (p. 1684.3) associated with herpes simplex infection a 5-day course of oral aciclovir at the start of the infection has been proposed to prevent the subsequent skin lesions.[1] If this fails, a 6-month course of oral aciclovir has been found to be of benefit,[2] even if the association with herpes is not obvious. It should be noted, however, that erythema multiforme may occur as an adverse effect of systemic aciclovir.

1. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128**: 542–5.
2. Tatnall FM, *et al.* A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol* 1995; **132**: 267–70.

HIV infection. Herpes simplex virus type 2 (HSV-2) seroprevalence among HIV-1 infected persons ranges from 50 to 90%. HSV-2 reactivations are common and often asymptomatic among HIV-1 infected persons. During HSV-2 reactivations plasma and genital HIV-1 levels increase and may increase HIV-1 transmissibility and disease progression. HSV-2 suppression has therefore been considered as a potential strategy to reduce HIV-1 viral load, slow HIV-1 disease progression, and possibly delay the need to start HAART.[1] Randomised studies[2-5] among

HIV-1 and HSV-2 co-infected persons not taking antiretroviral therapy (ART) and not severely immunocompromised found that standard HSV-2 suppressive therapy with oral aciclovir (400 mg twice daily) or oral valaciclovir (500 mg twice daily) for 8 to 12 weeks significantly reduced plasma and genital HIV-1 levels. However, another study[4] reported that standard suppressive treatment with oral aciclovir for 12 weeks had no effect on the rate of HIV genital shedding despite a reduction in genital HSV-2. A further study[7,8] in southern and east Africa in heterosexual, discordant (for HIV-1) couples where one partner was co-infected with HSV-2 and HIV-1, had a CD4 + count of 250 cells/microlitre or more, and was not taking ART, reported that standard daily suppressive treatment for HSV-2 with oral aciclovir, given for up to 24 months, reduced the risk of HIV-1 disease progression by 16% when compared with placebo treatment.[7] However, the incidence of transmission of HIV-1 to the previously uninfected sexual partner was not reduced.[8]

1. Tan DH, *et al.* Can herpes simplex virus type 2 suppression slow HIV disease progression: a study protocol for the valacyclovir in delaying antiretroviral treatment entry (VALIDATE) trial. *Trials* 2010; 11: 113.
2. Nagot N, *et al.* Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007; 356: 790–9.
3. Zuckerman RA, *et al.* Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. *J Infect Dis* 2007; 196: 1500–8.
4. Baeten JM, *et al.* Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. *J Infect Dis* 2008; 198: 1804–8.
5. Delany S, *et al.* Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. *AIDS* 2009; 23: 461–9.
6. Cowan FM, *et al.* A randomised placebo-controlled trial to explore the effect of suppressive therapy with acyclovir on genital shedding of HIV-1 and herpes simplex virus type 2 among Zimbabwean sex workers. *Sex Transm Infect* 2008; 84: 548–53.
7. Lingappa JR, *et al.* Daily acyclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet* 2010; 375: 824–33.
8. Celum C, *et al.* Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010; 362: 427–39.

Adverse Effects

Aciclovir is generally well tolerated. When given intravenously as aciclovir sodium it may cause local reactions at the injection site with inflammation and phlebitis; these reactions may be associated with extravasation that can lead to tissue necrosis.

Renal impairment may be associated with systemic use of aciclovir in some patients; it is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. The risk of renal toxicity is increased by conditions favouring deposition of aciclovir crystals in the tubules such as when the patient is poorly hydrated or has existing renal impairment, or when the drug is given at a high dosage or by rapid or bolus injection. Some patients taking systemic aciclovir may have transient increases in blood concentrations of urea and creatinine although this is more acute with intravenous dosage.

Occasional adverse effects after systemic use include increased serum bilirubin and liver enzymes, haematological changes, rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), fever, headache, dizziness, and gastrointestinal effects such as nausea, vomiting, and diarrhoea. Hepatitis and jaundice have been reported rarely. Anaphylaxis and angioedema have occurred. Reversible neurological effects including lethargy, somnolence, confusion, hallucinations, agitation, tremors, psychosis, convulsions, and coma have been reported in a small number of patients, particularly in those given intravenous aciclovir and with predisposing factors such as renal impairment; these effects may be more marked in older patients. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, sometimes resulting in death, have occurred in immunocompromised patients given high parenteral doses of aciclovir. Accelerated diffuse hair loss has also been reported.

Topical application of aciclovir may produce transient stinging, burning, itching, or erythema. Eye ointments may occasionally produce transient stinging, superficial punctate keratopathy, blepharitis, or conjunctivitis.

Effects on the blood. There has been no evidence of bone-marrow toxicity in patients given aciclovir after bone marrow transplantation.[1,2] However, megaloblastic haematopoiesis was seen in the bone marrow of 3 patients given aciclovir for suspected or proven herpes simplex encephalitis.[3] There has also been a report of inhibition of human peripheral blood lymphocytes in samples taken from healthy subjects given aciclovir.[4]

1. Serota FT, *et al.* Acyclovir treatment of herpes zoster infections: use in children undergoing bone marrow transplantation. *JAMA* 1982; 247: 2132–5.
2. Gluckman E, *et al.* Oral acyclovir prophylactic treatment of herpes simplex infection after bone marrow transplantation. *J Antimicrob Chemother* 1983; 12 (suppl B): 161–7.
3. Amos RJ, Amess JAL. Megaloblastic haemopoiesis due to acyclovir. *Lancet* 1983; i: 242–3.
4. Tauris P, *et al.* Evaluation of the acyclovir-induced modulation of the plaque-forming cell response of human peripheral blood lymphocytes. *J Antimicrob Chemother* 1984; 13: 71–7.

Effects on the kidneys. Aciclovir is excreted mostly by the kidney, and reaches high concentrations in the tubular lumen, but is relatively insoluble in urine and may therefore cause intratubular precipitation of crystals in the kidney and renal damage which may result in acute renal failure within 24 to 48 hours. High doses, dehydration, or pre-existing renal impairment increase the risk of aciclovir-associated acute renal failure, which has been reported in 12 to 48% of patients in some series. Although usually asymptomatic there may be nausea, vomiting, and flank pain, together with haematuria and pyuria. Most patients recover on stopping the drug and rehydration, though some need temporary dialysis; use of a loop diuretic may be helpful in some cases. Slow infusion and adequate hydration can help to prevent crystal precipitation, and doses should be reduced in patients with underlying renal impairment.[1-3] An obese man developed acute renal failure after seven 1-g doses (calculated according to his actual body-weight) of intravenous aciclovir. Aciclovir distributes mainly into water and therefore dosing based on actual rather than ideal body-weight may result in a significant overdose and thereby increase the risk for renal impairment.[2]

There are also occasional reports of renal toxicity apparently unrelated to crystal precipitation.[4-6]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; 106: 459–65.
2. Hernandez JO, *et al.* Acyclovir-induced renal failure in an obese patient. *Am J Health-Syst Pharm* 2009; 66: 1288–91.
3. Fleischer R, Johnson M. Acyclovir nephrotoxicity: a case report highlighting the importance of prevention, detection, and treatment of acyclovir-induced nephropathy. *Case Report Med* 2010; 2010: 602783.
4. Giustina A, *et al.* Low-dose acyclovir and acute renal failure. *Ann Intern Med* 1988; 108: 312.
5. Eck P, *et al.* Acute renal failure and coma after a high dose of oral acyclovir. *N Engl J Med* 1991; 325: 1178.
6. Johnson GL, *et al.* Acute renal failure and neurotoxicity following oral acyclovir. *Ann Pharmacother* 1994; 28: 460–3.

Effects on the nervous system. Neurotoxicity, including tremor, confusion, myoclonus, agitation, lethargy, or hallucination, is an uncommon adverse effect of aciclovir, and may be hard to distinguish from progression of the underlying disease state. Renal impairment may increase the risk, although no clear relationship with peak plasma concentrations has been shown; cases are also more common in elderly patients and those taking other neurotoxic drugs.[1] Of 143 patients given aciclovir by intravenous infusion in doses ranging from 0.75 to 3.6 g/m² daily for the treatment of herpesvirus infections after bone marrow transplantation, 6 developed reversible neurological symptoms including tremor, agitation, nausea, lethargy, mild disorientation, autonomic instability, hemiparaesthesia, and slurred speech.[2] EEGs were diffusely abnormal in all 6. Symptoms improved in all patients on withdrawing aciclovir; reinstituting aciclovir in 2 produced a recurrence of symptoms. Concomitant therapy included irradiation and methotrexate intrathecally for all 6, interferon alfa for 3, and ciclosporin for 1. It has been suggested that if it is difficult to distinguish worsening encephalitis from aciclovir neurotoxicity, a trial of haemodialysis might be appropriate.[3] Development of neurotoxic symptoms has been reported[4] to be associated with increased concentrations of the metabolite 9-carboxymethoxymethylguanine in serum and CSF.

1. Ernst ME, Franey RJ. Acyclovir- and ganciclovir-induced neurotoxicity. *Ann Pharmacother* 1998; 32: 111–13.
2. Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. *Ann Intern Med* 1983; 98: 921–5.
3. Brady M, Main J. Aciclovir neurotoxicity is an important side effect of therapy in patients with renal impairment. *Clin Med* 2009; 9: 630. Correction, *ibid.* 2010; 10: 205.
4. Helldén A, *et al.* The aciclovir metabolite CMMG is detectable in the CSF of subjects with neuropsychiatric symptoms during aciclovir and valaciclovir treatment. *J Antimicrob Chemother* 2006; 57: 945–9.

Effects on the skin. Vesicular or bullous lesions have been associated with intravenous use of aciclovir in patients thought to have herpes simplex encephalitis.[1,2] Careful evaluation is necessary to differentiate the reaction from herpetic lesions. Recall dermatitis in an area previously affected by herpes zoster lesions has also been associated with aciclovir.[3]

See also Hypersensitivity, below.

1. Buck ML, *et al.* Vesicular eruptions following acyclovir administration. *Ann Pharmacother* 1993; 27: 1458–9.
2. Armingaud P, *et al.* Eruption bulleuse localisée après injection intraveineuse d'aciclovir: mécanisme toxique ou immunoallergique? *Ann Dermatol Venereol* 2000; 127: 496–8.
3. Carrasco L, *et al.* Drug eruption secondary to aciclovir with recall phenomenon in a dermatome previously affected by herpes zoster. *Clin Exp Dermatol* 2002; 27: 132–4.

Hypersensitivity. Hypersensitivity reactions,[1-3] including maculopapular rash and itching, anaphylaxis, and angioedema have been associated with the use of aciclovir. Cross-sensitivity to famciclovir[4] and to the prodrug valaciclovir[5,6] may occur; although some patients hypersensitive to aciclovir have been treated with famciclovir as an alternative.[7] Successful induction of tolerance to oral aciclovir has been described.[1,4]

1. Henry RE, *et al.* Successful oral acyclovir desensitization. *Ann Allergy* 1993; 70: 386–8.
2. Schuster J, *et al.* Allergic drug eruption secondary to intravenous acyclovir. *Acta Derm Venereol* 2008; 88: 196–8.
3. Jen SP, *et al.* Probable acyclovir-induced angioedema in a patient with HIV infection and suspected varicella-zoster virus encephalitis. *Am J Health-Syst Pharm* 2011; 68: 2257–60.
4. Kawsar M, *et al.* Graded challenge in an aciclovir allergic patient. *Sex Transm Infect* 2001; 77: 204–5.
5. Lammintausta K, *et al.* Rapid systemic valaciclovir reaction subsequent to aciclovir contact allergy. *Contact Dermatitis* 2001; 45: 181.
6. Ebo DG, *et al.* Immediate allergy from valacyclovir. *Allergy* 2008; 63: 941–2.
7. Bayrou O, *et al.* Famciclovir as a possible alternative treatment in some cases of allergy to acyclovir. *Contact Dermatitis* 2000; 42: 42.

Vasculitis. Aciclovir has been associated with vasculitis. In one patient[1] it was one of many drugs given that may have caused a necrotising vasculitis. In another report an immunocompromised child with chickenpox given aciclovir by infusion developed a vasculitic rash which diminished on withdrawal of the drug.[2]

For a report of peripheral neuropathy associated with vasculitis due to the prodrug valaciclovir, see Effects on the Nervous System, p. 1021.3.

1. von Schulthess GK, Sauter C. Acyclovir and herpes zoster. *N Engl J Med* 1981; 305: 1349.
2. Platt MPW, Eden OB. Vasculitis in association with chickenpox treatment in childhood acute lymphoblastic leukaemia. *Lancet* 1982; ii: 763–4.

Precautions

Systemic aciclovir should be used with caution and in reduced doses in patients with renal impairment (see Administration in Renal Impairment, p. 964.3). The elderly and patients with existing renal impairment should be closely monitored for neurological adverse effects. Adequate hydration should be maintained in patients given parenteral or high oral doses of aciclovir. Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir in the kidney; rapid or bolus injection should be avoided. The risk of renal impairment is increased by use with other nephrotoxic drugs. Doses of intravenous aciclovir based on actual body-weight may be excessive in obese patients, especially those with renal impairment; doses for obese patients should be calculated according to their ideal body-weight (see also under Effects on the Kidneys, above). Intravenous aciclovir should also be used with caution in patients with underlying neurological abnormalities, with significant hypoxia, or with serious hepatic or electrolyte abnormalities. In severely immunocompromised patients, prolonged or repeated courses of aciclovir may result in the selection of virus strains with reduced sensitivity; patients may, therefore, not respond to continued treatment.

Breast feeding. Aciclovir is distributed into breast milk[1-4] and in some instances concentrations are higher than in maternal serum.[1-3] Licensed product information reports that a maternal oral dose of 200 mg five times daily could expose a breast-fed infant to 300 micrograms/kg daily and advises caution when giving nursing mothers aciclovir. However, no adverse effects have been seen in breast-fed infants of mothers taking aciclovir, and the last available guidance from the American Academy of Pediatrics considered[5] that it was therefore usually compatible with breast feeding.

1. Lau RJ, *et al.* Unexpected accumulation of acyclovir in breast milk with estimation of infant exposure. *Obstet Gynecol* 1987; 69: 468–71.
2. Meyer LJ, *et al.* Acyclovir in human breast milk: *Am J Obstet Gynecol* 1988; 158: 586–8.
3. Bork K, Benes P. Concentration and kinetic studies of intravenous acyclovir in serum and breast milk of a patient with eczema herpeticum. *J Am Acad Dermatol* 1995; 32: 1053–5.
4. Taddio A, *et al.* Acyclovir excretion in human breast milk. *Ann Pharmacother* 1994; 28: 585–7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/04/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Pregnancy. The incidence of congenital abnormality and spontaneous fetal loss in 1246 cases of prenatal exposure to oral or intravenous aciclovir (as recorded by the International Acyclovir Pregnancy Registry between 1 June 1984 and 30 June 1998) did not significantly differ from

those in the general population.[1] A large population-based historical cohort study[2] of live-born infants in Denmark from January 1996 to September 2008 found exposure to oral aciclovir (1561 exposures), valaciclovir (229 exposures), or famciclovir (26 exposures) in the first trimester of pregnancy was not associated with an increased risk of major birth defects diagnosed within the first year of life. Forty of 1804 infants (2.2%) exposed to aciclovir, valaciclovir, or famciclovir in the first trimester were identified with a major birth defect compared with 19 920 of about 800 000 (2.4%) unexposed infants. Similarly, use of aciclovir cream in the first trimester of pregnancy was not associated with birth defects but there were too few exposures to penciclovir cream to evaluate its safety.

The Royal College of Obstetricians and Gynaecologists[3] recommends that systemic aciclovir may be given to pregnant women who present with a first episode of genital herpes, however, caution is advised when giving aciclovir before 20 weeks of gestation. Daily use over the last four weeks of pregnancy to reduce the risk of recurrence at term is, however, not routinely recommended. Due to an apparent increase in risk and severity of varicella pneumonitis in the latter half of pregnancy, the UK Advisory Group on Chickenpox[4] recommends oral aciclovir for all pregnant women with chickenpox who present within 24 hours of the onset of a rash if pregnancy is at more than 20 weeks of gestation.

1. Stone KM, *et al.* Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the International Acyclovir Pregnancy Registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol* 2004; 70: 201–7.
2. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA* 2010; 304: 859–66.
3. Royal College of Obstetricians and Gynaecologists. Green-top guideline no. 30: management of genital herpes in pregnancy (revised September 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT30GenitalHerpes2007.pdf (accessed 01/03/11)
4. Nathwani D, *et al.* Varicella infections in pregnancy and the newborn: a review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998; 36 (suppl 1): 59–71.

Sodium content. Each g of aciclovir sodium contains 4.05 mmol of sodium.

Interactions

Probenecid is reported to block the renal clearance of aciclovir. The risk of renal impairment is increased by use with other nephrotoxic drugs.

Antivirals. Use of *zidovudine* with aciclovir is not generally associated with additional toxicity.[1] However, there is a report[2] of a patient who had overwhelming fatigue when given aciclovir and zidovudine together; no such effect occurred when each drug was given alone.

Former product information for *interferon alfa-n1* reported progressive renal failure in patients also given aciclovir.

1. Tartaglione TA, *et al.* Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; 35: 2225–31.
2. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; 316: 547.

Theophylline. For reference to evidence that aciclovir inhibits *theophylline* metabolism, resulting in accumulation, see p. 1235.2.

Antiviral Action

Aciclovir is active against herpes simplex virus type 1 and type 2 and against varicella-zoster virus. This activity requires intracellular conversion of aciclovir by viral thymidine kinase to the monophosphate with subsequent conversion by cellular enzymes to the diphosphate and the active triphosphate. This active form inhibits viral DNA synthesis and replication by inhibiting the herpesvirus DNA polymerase enzyme as well as being incorporated into viral DNA. This process is highly selective for infected cells. Studies in *animals* and *in vitro* have found various sensitivities but show that target viruses are inhibited by concentrations of aciclovir that are readily achieved clinically. Herpes simplex virus type 1 appears to be the most susceptible, then type 2, followed by varicella-zoster virus.

The Epstein-Barr virus and CMV are also susceptible to aciclovir to a lesser extent. However, for CMV it does not appear to be activated by thymidine kinase and may act via a different mechanism. Epstein-Barr virus may have reduced thymidine kinase activity but its DNA polymerase is very sensitive to inhibition by aciclovir triphosphate, which may account for the partial activity.

Aciclovir has no activity against latent viruses, but there is some evidence that it inhibits latent herpes simplex virus at an early stage of reactivation.

Herpes simplex virus develops resistance to aciclovir *in vitro* and *in vivo* by selection of mutants deficient in thymidine kinase. Other mechanisms of resistance include altered substrate specificity of thymidine kinase and reduced sensitivity of viral DNA polymerase. Resistance has also been reported with varicella-zoster virus, probably by similar mechanisms.

Although occasional treatment failures have been reported, resistance has not yet emerged as a major problem in treating herpes simplex infections in immunocompetent patients. However, resistant viruses are more likely to be a problem in patients with a suppressed immune response.

There is virtually complete cross-resistance of herpes simplex strains between aciclovir and penciclovir, although it is not universal. Cross-resistance is also nearly universal between aciclovir and brivudine. However, cross-resistance is not usually seen in aciclovir-resistant thymidine kinase mutants to cidofovir, foscarnet, or vidarabine, which either do not require intracellular activation, or are not activated by thymidine kinase. If resistance does occur, it must be due to DNA polymerase mutation. Aciclovir-resistant thymidine-kinase mutants of herpes simplex are often cross-resistant to ganciclovir, whereas aciclovir-resistant polymerase mutants often retain sensitivity to the latter. Cross-resistance in strains of varicella zoster virus between aciclovir and penciclovir has been reported.

Resistance. References.

1. Bacon TH, *et al.* Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbiol Rev* 2003; 16: 114–28.
2. Malvy D, *et al.* A retrospective, case-control study of acyclovir resistance in herpes simplex virus. *Clin Infect Dis* 2005; 41: 320–6.

Pharmacokinetics

Aciclovir is poorly absorbed from the gastrointestinal tract after oral doses. Bioavailability of oral aciclovir is about 10 to 20%; orally active prodrugs such as valaciclovir (p. 1021.1) have been developed to overcome this poor absorption.

After intravenous dosage as aciclovir sodium it is widely distributed to body tissues and fluids including the CSF where concentrations are about 50% of those in plasma. Protein binding is reported to range from 9 to 33%.

Aciclovir is excreted largely unchanged in the urine, by glomerular filtration and some active tubular secretion, with up to 14% appearing in the urine as the inactive metabolite 9-carboxymethoxymethylguanine. In patients with normal renal function, the half-life is about 2 to 3 hours. In patients with chronic renal failure, this value is increased and may be up to 19.5 hours in anuric patients. During haemodialysis the half-life has been reported to be reduced to 5.7 hours, with 60% of a dose of aciclovir being removed. Faecal excretion may account for about 2% of a dose.

Probenecid increases the half-life and the area under the plasma concentration-time curve of aciclovir.

Aciclovir crosses the placenta and is distributed into breast milk in concentrations about 3 times higher than those in maternal serum.

Absorption of aciclovir is usually slight after topical application to intact skin, although it may be increased by changes in formulation. Aciclovir is absorbed after application of a 3% ointment to the eye giving a relatively high concentration in the aqueous humour but negligible amounts in the blood.

Reviews.

1. de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother* 1983; 12 (suppl B): 29–37.
2. Laskin OL. Clinical pharmacokinetics of acyclovir. *Clin Pharmacokinet* 1983; 8: 187–201.
3. Wagstaff AJ, *et al.* Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; 47: 153–205.

Distribution. The pharmacokinetics of oral aciclovir and its distribution into the eye.[1]

1. Hung SO, *et al.* Pharmacokinetics of oral acyclovir (Zovirax) in the eye. *Br J Ophthalmol* 1984; 68: 192–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acerpes; Acido; Aciclotex; Apofarm; Dioxis; Duolip; Lafevir; Lisovyr; Oralsone Herpes; Poviral; Trixviral; Virostatic; Xiclovir; Zovirax; *Austral.*: Acihexal; Acivir; Acydo-V; Blistex Antiviral; Chemists Own Cold Sore; Lovir; Nyal Antiviral Cold Sore; Ozvir; Zovirax; Zydlr†; *Austria*: Acic; Aciclobene; Aciclostad; Actvir; Herpomed; Nycovir†; ViroMed; Xorox; Zovirax; *Belg.*: Aciclomed; Docaclo†; Viratop; Zovirax; *Braz.*: Aciclolar; Aciclomed; Acilor; Aciveral; Advirax; Andomax; Antivirax; Aviral; Clovir; Ductovirax; Exavir; Ezopen; Heclivir; Herpesil; Hervirax; Hpvir; Uni Vir; Zovirax; *Canad.*: Zovirax; *Chile*: Eurovir; Lisovyr; Oftavir; Vironida; Zovirax; *China*: A Lun (阿仑); A Te Mi An (阿特米安); Ai Bei Qing (艾贝清); Ai Er Xin (爱尔新); Aisike (艾思克); Asile (阿思乐); Bangna (邦纳); Bao Zhen Kang (葆珍康); Bo Shi Duo Wei (博仕多为); De Er Li Wei (得尔力伟); Dong Yan Qi Rui (东药琦锐); Gantal (甘泰); He Gu (和谷); Jie Ke (洁珂); Jie Luo Wei (洁罗维); Jimin Weixin (济民维新); Kang Da Wei (康达威); Keduxing (克毒星); Li Ke Ping (丽科平); Li Ke Xin (丽科欣); Luo Fu (洛芙); Nai Ge (奈格); Qiang Ni (强尼); Qing Lin (清林); Sha Wei Luo (沙威洛); Sheng Nuo Wei (圣诺韦); Tiancheng Xi Er (天诚惜尔); Wei Ping (韦平); Wei Xin (韦信); Wei-Jia (唯甲); You Kang (佑康); Zhengda Jiepu (正大捷普); Zhu Li (注力); Zovirax (苏维乐); Zylovir (西洛伟); *Cz.*: Acyclostad; Herpesin; Provirsan; Ranvir†; Virolex†; Zovirax; *Denm.*: Acidolan; Acivir; Avirox; Geavir; Herpavir; Zovir; Zovirax; *Fin.*: Aciclad; Aclovir; Acyclostad; Acyrax; Antix; Herpolips; Zovirax; *Fr.*: Aciclovivax†; Activir; Herpevir; Kendix; Remex; Viruclim; Zovirax; *Ger.*: Acerpes†; Acic-Ophtal; Acic†; Acidot†; Acidoc beta; Aciclostad; Actvir†; ActVision; Supraviran†; Virupos; Vir-din; Zoliparin†; Zovirax; *Gr.*: Abduce; Amitrox; Biozirox; Cargosil; Cevinolon; Clovirax; Cycloviran; Erpaclovir; Erpizon; Etasten; Fibrilan; Hagevir; Helposol; Herzkur; Neldim; Pulibex; Unipex; Verpir; Virusteril; Xorox; Zeramil; Zicoten; Zidovimm; Zovirax; *Hong Kong*: Acilax; Aclovirax†; Avorax; Clinovir†; Cusiviral; Cyclovax; Declovir; Entir; Eurodovir; Panovir†; Lovir; Medovir; Qualidovir; Saforax†; Syncovir†; Vidaclovir†; Virest; Virocivar; Virucid; Wariviron†; Zevin†; Zoral; Zoraxin†; Zostin†; Zostinol†; Zovirax; *Hung.*: Acyclostad; Herpesin; Telviran; Viroex; Zovirax; *India*: Aciv; Acivir; ACV; Acviral; Alovir; Axovir; Cevirin; Civir; Cutivir; Cyclovir; Herperax; Herpex; Herpil; Herzovir; Kayvir; Koviran; Lovir; Nisivir; Ocurax; Ocuvir; Okavir; Ovir; Zovirax; *Indon.*: Acifar; Azovir†; Clinovir; Clopes; Danovir; Herax; Herpiclof; Kenrovir†; Licovir; Matrovir†; Molavir; Nevirz†; Palovir; Poviral; Quavir†; Scanovir; Temiral; Viralis; Vircella†; Vircovir; Virdam; Vireth; Virpes; Virtaz; Viruses; Zorel†; Zoter; Zovirax; Zumasid†; Zydorax; *Irl.*: Acic; Bellvir; Herpetad†; Soothelip; Viralief; Zovirax; *Israel*: Acivir; Acyclo-V; Acyclovenir; Cyclomed; Supra-Vir†; V-Ral; Zovirax; *Ital.*: Aciclin; Aciclinlabiale; ACV; Acyvir†; Alovir; Amodivyr; Avirasc; Avix; Avyclor; Avyplus; Cycloviran; Dravyr; Efriviral; Esavir; Euclivir†; Fuviron; Herpesnil; Iliador; Nedovir; Neviran; Riduvir; Sanavir; Voraclor; Zovirax; *Jpn*: Zovirax; *Malaysia*: Acyletec; Avorax; Cusiviral; Declovir; Hepirax; Herpevex; Lovir; Medovir; Vacrax; Virless; Virudd; Zevin; Zoral; Zoraxin; Zovirax; *Mex.*: Acifur†; Akevir; Apo-Vir; Avirex-T; Bioviraz; Brimex; Ciclofaron; Clirbest; Clociver; Clovex; Clyvorax; Dyskly; Epsin†; Erser; Firext†; Hercivir; Herpilem†; Isavir; Jersin†; Kerastil; Lackern; Landvir; Lesador; Madov; Opthavir; Seradc; Sinarden; Sopravir; Sovidor; Vidoran; Viclovir; Viremix; Virestat; Virgangel; Viroxil; Zirconia; Ziverone; Zovirax; *Neth.*: Acyclostad; Herpolips; Kruidvat Koortslipcreme; Zovirax; *Norw.*: Antix; Zovirax; *NZ*: Lovir; Viraban; Zolaten; Zovirax; *Philipp.*: Aciherpin; Acyhex†; Clovir; Cloviron; Covelay; Cyclostad; Herpex; Klozivex; Lovir; Terclovir†; Virest; Zealor; Zoteran; Zovirax; *Pol.*: Abtovir†; Acix; Antivir; Awirol†; Cusiviral†; Hascovir; Herpesan; Herpex; Heviran; Virolex; Viru-POS; Xorovir†; Zovirax; *Port.*: Acidosina; Aciclovax; Briclofar; Ciclovira; Divicil; Faulvir; Hermix-Sofex; Milavir; Vidovir†; Zov800; Zovirax; *Russ.*: Citovir (Цитовир); Cyclovir (Цикловир); Herperax (Герперакс); Herpesin (Герпесин)†; Herpevir (Герпевир)†; Lovir (Ловир); Medovir (Медовир); Provirsan (Провирсан); Virolex (Виролекс); Vivorax (Виворакс); Zovirax (Зовиракс); *S.Afr.*: Actab; Acitop; Activir; Cydivex; Lovire; Vyrohexal; Zovirax; *Singapore*: Avorax; Beatix-AX; Cusiviral; Declovir; Dravyr; Entir; Erfivirax; Lovir; Medovir; SP-Virac; Vacrax; Virest; Virless; Vivorax†; Zoral; Zorax; Zoraxin; Zovirax; *Spain*: Aciclostad; Bel Labial†; Herpial; Maynar; Virherpes; Virment†; Viruderm; Zovicrem; Zovirax; *Swed.*: Anvir; Geavir; Zovirax; *Switz.*: Acivir; Aviral; Helvevir; Virucalm; Zovirax; *Thai.*: ACV; Acyvir; Azovax; Azycin†; Clinovir; Clovir; Clovira; Colsor; Covir; Cyclorax†; Declovir; Entir; Falerm; Herpenpon; Herperax; Herpirax; Herpizyg; Lermex; M-Zavir; Marvir; Monirax; Norum; Paviria; Ranvir; Reclovax; Vermis; Vilermo; Viraxy; Virless; Virofik; Virogon; Virolan†; Viromed; Vironil; Vivax†; Vivir; Vizo; Zevin; Zocovin; Zovirax; Zyvirpac; *Turk.*: Acyl; Aklovir; Asiviral; Hermovir; Herpeks†; Klovireks-L; Provir; Silovir; Virosil; Virupos; Xorox; Zovirax; *UAE*: Lovrak; *UK*: Aviral†; Clearsore; Cymex Ultra; Herpetad; Soothelip; Virasorb; Virovir; Zovirax; *Ukr.*: Acic (Ацик); Acivir (Ацивир); Herpevir (Герпевир); Heviran (Гевиран); Virolex (Виролекс); Zovirax (Зовиракс); *USA*: Sitavig; Xerese; Zovirax; *Venez.*: Acidor; Avir; Cloryvil; Herpin; Zovirax.

Multi-ingredient Preparations. *Cz.*: Xerclear; *Denm.*: Xerclear; *India*: Clovirax; *Rus.*: Herpferon (Герпферон); *Swed.*: Xerclear; *Ukr.*: Herpferon (Герпферон)†.

Pharmacopoeial Preparations

BP 2014: Aciclovir Cream; Aciclovir Eye Ointment; Aciclovir Infusion; Aciclovir Oral Suspension; Aciclovir Tablets; Dispersible Aciclovir Tablets;

USP 36: Acyclovir Capsules; Acyclovir for Injection; Acyclovir Ointment; Acyclovir Oral Suspension; Acyclovir Tablets.

Adefovir *(BAN, USAN, rINN)*

Adefovir; Adefovirum; GS-0393; PMEA; Адефовир.

[[2-(6-Amino-9*H*-purin-9-yl)ethoxy]methyl]phosphonic acid; 9-[2-(Phosphonomethoxy)ethyl]adenine.

$C_8H_{12}N_5O_4P$=273.2

CAS — 106941-25-7.

ATC — J05AF08.

ATC Vet — QJ05AF08.

UNII — 6GQP90I798.

Adefovir Dipivoxil (BANM, USAN, rINNM)

Adefovir Dipivoksil; Adéfovir Dipivoxil; Adefovir, dipivoxilo de; Adefovirum Dipivoxilum; *Bis* (POM)PMEA; Dipivoxilo de adefovir; GS-0840; Piv2PMEA; Адефовир Дипивоксил.

9-[2-({Bis[(pivaloyloxy)methoxy]phosphinyl}methoxy)ethyl] adenine.

$C_{26}H_{32}N_5O_8P$=501.5

CAS — 142340-99-6.

ATC — J05AF08.

ATC Vet — QJ05AF08.

UNII — U6Q8Z01514.

Uses and Administration

Adefovir is a nucleotide reverse transcriptase inhibitor, structurally related to adenine, that is given orally as the prodrug adefovir dipivoxil for the treatment of chronic **hepatitis B** (p. 952.1). It is used in adults with decompensated liver disease, or with compensated liver disease with evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of adefovir dipivoxil is 10 mg once daily. For details of dosage modification in patients with renal impairment, see below.

Adefovir was initially investigated for the treatment of **HIV infection**, but its use is limited by nephrotoxicity due to the high doses needed.

References.

1. Dando TM, Plosker GL. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; 63: 2215–34.
2. Rivkin AM. Adefovir dipivoxil in the treatment of chronic hepatitis B. *Ann Pharmacother* 2004; 38: 625–33.
3. Danta M, Dusheiko G. Adefovir dipivoxil: review of a novel acyclic nucleoside analogue. *Int J Clin Pract* 2004; 58: 877–86.
4. Jones J, *et al.* Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. *Health Technol Assess* 2009; 13: 1–172.

Administration in renal impairment. The oral dose of adefovir dipivoxil should be reduced in patients with renal impairment. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: usual 10 mg once-daily dosage (above)
- CC 30 to 49 mL/minute: 10 mg every 48 hours
- CC 10 to 29 mL/minute: 10 mg every 72 hours
- haemodialysis patients: 10 mg every 7 days after dialysis

Adverse Effects

The most common adverse effects reported from adefovir have been gastrointestinal effects including nausea, flatulence, diarrhoea, dyspepsia, vomiting, and abdominal pain. Other common adverse effects are headache and asthenia. There have also been reports of pruritus and skin rashes. Increases in serum-creatinine concentrations may occur and there have been instances of renal impairment and acute renal failure; proximal renal tubulopathy, Fanconi syndrome, and hypophosphataemia have also been reported. Raised liver enzyme concentrations may occur and severe acute exacerbation of hepatitis has been reported after stopping treatment with adefovir.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p. 1024.3).

Precautions

Adefovir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Adefovir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients whose liver enzyme values increase due to response to treatment must be distinguished from those in whom these indicate toxicity. Exacerbation of hepatitis has been reported in patients who developed resistance to adefovir and in those who stopped adefovir; patients who stop treatment should be monitored closely for an appropriate period. In order to minimise the risk of resistance in patients with lamivudine-resistant hepatitis B, adefovir should be used with lamivudine and not as monotherapy. Patients taking adefovir with normal renal function should be monitored every 3 months for signs of deteriorating renal function; patients at risk of renal impairment should be monitored more frequently and particular care should be exercised in patients with a creatinine clearance of less than 50 mL/minute, who may require dosage modification, and in those receiving other drugs that may affect renal function.

Use of adefovir to treat chronic hepatitis B infection in patients with undiagnosed or untreated HIV infection may result in the emergence of resistant strains of HIV. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with adefovir.

Breast feeding. It is unknown whether adefovir is distributed into breast milk but licensed product information recommends that mothers should not breast feed if taking adefovir.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adefovir dipivoxil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Studies in *rodents* given high intravenous doses of adefovir (systemic exposure 38 times that in the human) have found it to be fetotoxic or embryotoxic; neither high oral doses (systemic exposure 23 to 40 times that in the human) nor lower intravenous doses (systemic exposure 12 times that in the human) produced evidence of teratogenicity or embryotoxicity. There are no studies available on the use of adefovir in pregnant women and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk.

Interactions

Caution should be exercised when adefovir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug. Care is required when adefovir is given with other drugs with the potential for nephrotoxicity; licensed product information advises against use with tenofovir.

Antiviral Action

Adefovir is converted intracellularly in stages to the diphosphate, which then inhibits the DNA synthesis of hepatitis B virus through competitive inhibition of reverse transcriptase and incorporation into viral DNA. At high doses it has some activity against HIV.

Antiviral resistance. The development of antiviral resistance is a concern with long-term nucleoside or nucleotide treatment for chronic hepatitis B. Studies[1-4] in patients with chronic hepatitis B showed no resistance to adefovir after 1 year of treatment, but resistance rates increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively. Adefovir was found to be effective in patients who had previously developed resistance to lamivudine.[4]

1. Marcellin P, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; 348: 808–16. Correction. *ibid.*: 1192.
2. Hadziyannis SJ, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; 348: 800–7. Correction. *ibid.*: 1192.
3. Hadziyannis SJ, *et al.* Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005; 352: 2673–81.
4. Delaney WE. Progress in the treatment of chronic hepatitis B: long-term experience with adefovir dipivoxil. *J Antimicrob Chemother* 2007; 59: 827–32.

Pharmacokinetics

After oral doses adefovir dipivoxil is rapidly converted to adefovir. Peak plasma concentrations of adefovir occur after about 0.6 to 4 hours. Bioavailability is reported to be 59% after a single oral dose. Absorption is delayed but not reduced when given with food. Adefovir is widely distributed to body tissues, particularly into the kidneys, liver, and intestines. Less than 4% is bound to plasma or serum proteins. Adefovir is excreted renally by glomerular filtration and active tubular secretion; the terminal elimination half-life is reported to be about 7 hours. Adefovir is partially removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biovir; Hepsera; Revervir†; *Austral.*: Hepsera; *Austria*: Hepsera; *Belg.*: Hepsera; *Braz.*: Hepsera; *Canad.*: Hepsera; *Chile*: Hepsera; *China*: A Di Xian (阿迪仙); A Gan Ding (阿甘定); Ailuwei (爱路韦); Dai Ding (代丁); Dinghe (丁贺); Hepsera (贺维力); Lifuzhi (利福之); Ming Zheng (名正); Xinfunuo (欣复诺); Yilaifen (亿来芬); Youheding (优贺丁); Yue Bao (粤宝); *Cz.*: Hepsera; *Denm.*: Hepsera; *Fin.*: Hepsera; *Fr.*: Hepsera; *Ger.*: Hepsera; *Gr.*: Hepsera; *Hong Kong*: Hepsera; *Hung.*: Hepsera; *India*: Adesera; Adfovir; Adheb; *Indon.*: Hepsera; *Irl.*: Hepsera; *Israel*: Hepsera; *Ital.*: Hepsera; *Malaysia*: Hepsera; *Mex.*: Hepsera; *Neth.*: Hepsera; *Norw.*: Hepsera; *NZ*: Hepsera; *Philipp.*: Hepsera; *Pol.*: Hepsera; *Port.*: Hepsera; *Singapore*: Hepsera; *Spain*: Hepsera; *Swed.*: Hepsera; *Switz.*: Hepsera; *Thai.*: Hepsera; *Turk.*: Hepsera; *UK*: Hepsera; *USA*: Hepsera; *Venez.*: Hepsera.

Amprenavir (BAN, USAN, rINN)

141W94; Amprenaviiri; Amprénavir; Amprenavirum; Amprenawir; KVX-478; VX-478; Ампренавир.

(3*S*)-Tetrahydro-3-furyl[(*1S*)-α-[(*1R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl]carbamate.

$C_{25}H_{35}N_3O_6S$=505.6

CAS — 161814-49-9.

ATC — J05AE05.

ATC Vet — QJ05AE05.

UNII — 5S0W860XNR.

Uses and Administration

Amprenavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when amprenavir is used alone, and it is therefore used with other antiretrovirals.

Amprenavir has been given orally as capsules or solution but the bioavailability of these formulations (*Agenerase, GlaxoSmithKline*) differ and their doses are not interchangeable.

- In adults and adolescents (13 to 16 years) weighing 50 kg or more the *capsules* have been given in a dose of 1.2 g twice daily; when given with ritonavir (ritonavir-boosted amprenavir) the recommended dose is amprenavir 600 mg with ritonavir 100 mg twice daily or amprenavir 1.2 g with ritonavir 200 mg once daily.
- The *oral solution* has been given in a dose of 17 mg/kg three times daily (maximum daily dose 2.8 g) or 1.4 g twice daily.

For details of doses in children and patients weighing less than 50 kg, see below. For dosage in hepatic impairment, also see below.

Amprenavir is now mostly used in the form of the prodrug fosamprenavir (see p. 980.1), which may aid compliance by reducing adverse effects and increasing flexibility of dosing.

Reviews.

1. Noble S, Goa KL. Amprenavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; 60: 1383–1410.
2. Arvieux C, Tribut O. Amprenavir or fosamprenavir plus ritonavir in HIV infection: pharmacology, efficacy and tolerability profile. *Drugs* 2005; 65: 633–59.

Administration in children. For the treatment of HIV infection in children 4 to 12 years of age and in adolescents (13 to 16 years) weighing less than 50 kg, amprenavir has been given daily with other antiretroviral drugs. Doses are based on body-weight:

- the *capsules* in an oral dose of 20 mg/kg twice daily or 15 mg/kg three times daily, to a maximum daily dose of 2.4 g, or
- the *solution* in an oral dose of 22.5 mg/kg twice daily or 17 mg/kg three times daily, to a maximum daily dose of 2.8 g

Administration in hepatic impairment. Amprenavir should be used with caution and in reduced doses in patients with hepatic impairment. Additionally, the oral solution contains propylene glycol and extra restrictions may apply.

The following doses have been recommended in UK licensed product information:

oral solution:

- do not use

capsules:

- moderate impairment: 450 mg twice daily
- severe impairment: 300 mg twice daily

The following doses have been recommended in US product information:

oral solution:

- Child-Pugh score 5 to 8: 513 mg twice daily
- Child-Pugh score 9 to 12: 342 mg twice daily
- hepatic failure: do not use

capsules:

- Child-Pugh score 5 to 8: 450 mg twice daily
- Child-Pugh score 9 to 12: 300 mg twice daily

Adverse Effects

As for Fosamprenavir, p. 980.3.

Precautions

As for Fosamprenavir, p. 980.3. For further information on cross-reactivity between sulfonamide drugs see Hypersensitivity, under Sulfamethoxazole, p. 365.3. The oral solution and capsule formulations of amprenavir (*Agenerase, GlaxoSmithKline*) also provide high daily doses of vitamin E (with its attendant adverse effects, see p. 2121.2). The oral solution has a high content of propylene glycol, present as an excipient, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further

information on propylene glycol toxicity, see Adverse Effects and Precautions, p. 2205.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amprenavir as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Amprenavir has been associated with teratogenicity in *animals*. The solution is contra-indicated in pregnancy due to the high propylene glycol content.

Interactions

As for Fosamprenavir, p. 980.3.

Agenerase oral solution (*GlaxoSmithKline*) is contra-indicated in patients taking disulfiram or other products that reduce alcohol metabolism (such as metronidazole) and in those taking alcohol-containing products (such as ritonavir oral solution) because of the potential risk of toxicity from its propylene glycol content.

Antiviral Action

As for Fosamprenavir, p. 980.3.

Pharmacokinetics

Amprenavir is rapidly and well absorbed from the gastrointestinal tract after oral doses. Absorption is impaired by ingestion with a high-fat meal. Amprenavir capsules and oral solution are not bioequivalent; oral bioavailability is about 14% lower from the oral solution formulation than from the capsule formulation (*Agenerase, GlaxoSmithKline*). Peak plasma concentrations occur 1 to 2 hours after a single dose. It is about 90% bound to plasma proteins. Amprenavir is metabolised by hepatic cytochrome P450 isoenzyme CYP3A4. It is excreted mainly in the faeces as metabolites. The plasma elimination half-life is 7.1 to 10.6 hours.

References.

1. Sadler BM, Stein DS. Clinical pharmacology and pharmacokinetics of amprenavir. *Ann Pharmacother* 2002; 36: 102–18.
2. Stein DS, *et al.* Pharmacokinetic and pharmacodynamic analysis of amprenavir-containing combination therapy in HIV-1-infected children. *J Clin Pharmacol* 2004; 44: 1301–8.
3. Yogev R, *et al.* Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother* 2005; 49: 336–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agenerase; *Austral.*: Agenerase; *Austria*: Agenerase†; *Braz.*: Agenerase; *Chile*: Agenerase†; *Cz.*: Agenerase†; *Fin.*: Agenerase†; *Ger.*: Agenerase†; *Gr.*: Agenerase; *Irl.*: Agenerase†; *Israel*: Agenerase; *Mex.*: Agenerase†; *Neth.*: Agenerase†; *NZ*: Agenerase; *Pol.*: Agenerase†; *Port.*: Agenerase†; *Rus.*: Agenerase (Агенераза); *Spain*: Agenerase†; *Switz.*: Agenerase†; *Turk.*: Agenerase†; *Venez.*: Agenerase.

Atazanavir Sulfate *(BANM, USAN, rINNM)*

Atazanavir, Sulfate d'; Atazanavir, sulfato de; Atazanavir Sulphate; Atazanaviri Sulfas; BMS-232632-05; BMS-232632 (atazanavir); Sulfato de atazanavir; Атазанавира Сульфат.

Dimethyl (3*S*,8*S*,9*S*,12*S*)-9-benzyl-3,12-di-*tert*-butyl-8-hydroxy-4,11-dioxo-6-(*p*-2-pyridylbenzyl)-2,5,6,10,13-pentaazatetradecanedioate sulfate (1:1).

$C_{38}H_{52}N_6O_7.H_2SO_4$=802.9.

CAS — 198904-31-3 (atazanavir); 229975-97-7 (atazanavir sulfate).

ATC — J05AE08.

ATC Vet — QJ05AE08.

UNII — 4MT4VIE29P.

Uses and Administration

Atazanavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when atazanavir is used alone, and it is therefore used with other antiretrovirals.

Atazanavir is given orally as the sulfate with food, but doses are expressed in terms of atazanavir; 228 mg of atazanavir sulfate is equivalent to about 200 mg of atazanavir.

The usual adult dose in both treatment-naive and treatment-experienced patients is atazanavir 300 mg, given with ritonavir 100 mg, once daily. In the USA, unboosted atazanavir 400 mg once daily may also be considered for treatment-naive patients who are unable to tolerate ritonavir.

Atazanavir should generally be ritonavir-boosted if it must be given with efavirenz, tenofovir, H_2-receptor antagonists, or proton pump inhibitors. While the use of atazanavir with efavirenz is generally not recommended (see Interactions, below) increasing the dose of atazanavir to 400 mg (with ritonavir 100 mg) once daily for use with efavirenz is considered acceptable in the USA for treatment-naive patients only. Atazanavir 400 mg with ritonavir 100 mg once daily has also been suggested when use with an H_2-receptor antagonist with tenofovir cannot be avoided, and UK licensed product information also suggests this regimen if use with a proton pump inhibitor or high-dose H_2-receptor antagonist (exceeding the equivalent of famotidine 40 mg/day) is essential.

For details of doses in children and adolescents, see below.

For details of recommended doses of atazanavir in patients with hepatic or renal impairment, see below and below respectively.

Reviews.

1. Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis* 2004; 38: 1599–1604.
2. Musial BL, *et al.* Atazanavir: a new protease inhibitor to treat HIV infection. *Am J Health-Syst Pharm* 2004; 61: 1365–74.
3. Orrick JJ, Steinhart CR. Atazanavir. *Ann Pharmacother* 2004; 38: 1664–74.
4. Swainston Harrison T, Scott LJ. Atazanavir: a review of its use in the management of HIV infection. *Drugs* 2005; 65: 2309–36.
5. Croom KF, *et al.* Atazanavir: a review of its use in the management of HIV-1 infection. *Drugs* 2009; 69: 1107–40.
6. Bentué-Ferrer D, *et al.* Clinical pharmacology, efficacy and safety of atazanavir: a review. *Expert Opin Drug Metab Toxicol* 2009; 5: 1455–68.

Administration in children. For the treatment of HIV infection in children 6 years of age and older and adolescents, atazanavir is given orally with food. Doses are based on body-weight.

In the USA the recommended dosage of atazanavir with ritonavir in *treatment-naive* patients at least 6 years of age is:

- 15 to 24 kg: atazanavir 150 mg once daily with ritonavir 80 mg once daily
- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

For *treatment-naive* patients at least 13 years of age and 39 kg, who are unable to tolerate ritonavir, the recommended dose is atazanavir 400 mg once daily.

The recommended dosage of atazanavir with ritonavir in *treatment-experienced* patients at least 6 years of age is:

- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

Although the overall range of doses recommended in the UK is the same as in the US, fewer body-weight divisions are suggested.

Administration in hepatic impairment. In treatment-naive patients the oral dose of atazanavir should be adjusted in hepatic impairment as follows:

- mild hepatic impairment (Child-Pugh category A): use with caution (no specific reduction recommended)
- moderate impairment (Child-Pugh category B): atazanavir 300 mg daily
- severe hepatic impairment (Child-Pugh category C): not recommended

Ritonavir-boosted atazanavir regimens should be used with caution in patients with mild hepatic impairment and should not be used in those with moderate to severe hepatic impairment.

Administration in renal impairment. Oral dose adjustments are not usually necessary for patients with renal impairment. However, US licensed product information recommends that treatment-naive patients on haemodialysis should be given atazanavir 300 mg once daily with ritonavir 100 mg once daily and that atazanavir should not be used in treatment-experienced patients on haemodialysis.

Adverse Effects

Commonly reported adverse effects of moderate or greater intensity associated with antiretroviral regimens containing atazanavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, and jaundice), headache, insomnia, and peripheral neurological symptoms, and scleral icterus. Other commonly reported adverse effects are asthenia and fatigue. Mild to moderate rashes (usually maculopapular) generally occurring after 8 weeks of treatment and resolving within 1 to 2 weeks have been reported. Stevens-Johnson syndrome and erythema multiforme have also been reported in patients given atazanavir. Atazanavir may prolong the PR interval of the ECG and asymptomatic first-degree AV block has been reported in some patients. There have also been rare reports of QT interval prolongation and torsade de pointes. Cases of nephrolithiasis have occurred. Most patients taking atazanavir have asymptomatic elevations in unconjugated bilirubin, which is reversible upon stopping treatment. Other abnormal laboratory results include elevated amylase and lipase, elevated liver enzymes, and low neutrophils.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including atazanavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including atazanavir. Metabolic abnormalities such as insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported; unboosted atazanavir generally does not appear to have a negative effect on lipid levels. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

In the USA, atazanavir is contra-indicated in patients with severe hepatic impairment, and UK licensed product information advises that use in those with moderate liver impairment should also be avoided. It should be used with caution, and liver enzymes values monitored, in patients with milder liver disease. The use of ritonavir-boosted atazanavir has not been studied in hepatic impairment; while US licensed product information recommends avoiding use in patients with any degree of hepatic insufficiency, UK licensed product information allows use, with caution, in those with mild impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Caution should be exercised in patients with pre-existing cardiac conduction disorders or in those taking drugs that prolong the PR or increase the QT intervals. Patients developing jaundice or scleral icterus associated with hyperbilirubinaemia should be tried on an alternative antiretroviral; dose reductions of atazanavir should not be considered.

Pregnancy. Atazanavir has not been associated with teratogenicity in *animals*. Although there are theoretical concerns that atazanavir given to mothers may exacerbate physiologic hyperbilirubinaemia and lead to kernicterus in neonates and young infants, these effects have so far not occurred in clinical studies.[1]

For further information on the use of HIV-protease inhibitors in pregnancy, see under Indinavir, p. 987.1.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 05/10/09)

Interactions

Atazanavir is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and inhibits CYP3A4, CYP2C8, and UGT1A1. Use with drugs mainly metabolised by these isoenzymes may result in increases in their plasma concentrations, while drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations. When ritonavir-boosted atazanavir is given, the drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of atazanavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- antiarrhythmics (amiodarone, bepridil, and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)

- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated.

Owing to the potential for increased serum concentrations of sildenafil, atazanavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, atazanavir may increase serum concentrations of inhaled fluticasone and salmeterol and combination with either is not recommended. Ritonavir-boosted atazanavir should not be used with drugs having narrow therapeutic windows that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide and propafenone. Proton pump inhibitors, the NNRTIs efavirenz and nevirapine, rifampicin, and St John's wort decrease the concentration of atazanavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance. H_2-receptor antagonists may also substantially reduce serum concentrations of atazanavir. Careful consideration needs to be given to both the size and timing of the H_2-receptor antagonist dose when use with atazanavir is required, and where the antiretroviral regimen also includes tenofovir, use with a H_2-receptor antagonist is best avoided entirely. For information on doses used in management of drug interactions, see Uses and Administration, p. 968.1.

Atazanavir should also not be given to patients taking indinavir, as indirect hyperbilirubinaemia may result. Atazanavir is also contra-indicated with irinotecan as atazanavir's inhibition of UGT1A1 may increase irinotecan toxicity.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Atazanavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Atazanavir is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur after 2 to 2.5 hours. On multiple dosing with a ritonavir-boosted regimen peak plasma concentrations occur after 3 hours. Bioavailability (of both ritonavir-boosted and non-boosted regimens) is enhanced if given with food. Atazanavir is reported to be 86% bound to serum proteins. It is distributed into semen and into the CSF. Atazanavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme family CYP3A; the metabolites appear to be inactive. Atazanavir is mainly excreted in faeces, mostly as metabolites, and to a smaller extent in the urine. The terminal elimination half-life of atazanavir is reported to be about 7 hours and 8.6 hours after a ritonavir-boosted regimen.

Reviews.

1. Le Tiec C, *et al.* Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet* 2005; **44**: 1035–50.
2. Avihingsanon A, *et al.* A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. *Clin Pharmacol Ther* 2009; **85**: 402–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Reyataz; ***Austral.***: Reyataz; ***Austria***: Reyataz; ***Belg.***: Reyataz; ***Braz.***: Reyataz; ***Canad.***: Reyataz; ***Chile***: Reyataz; ***China***: Reyataz (悦艾妥); ***Cz.***: Reyataz; ***Denm.***: Reyataz; ***Fin.***: Reyataz; ***Fr.***: Reyataz; ***Ger.***: Reyataz; ***Gr.***: Reyataz; ***Hong Kong***: Reyataz; ***Hung.***: Reyataz; ***India***: Atazor; ***Indon.***: Reyataz†; ***Irl.***: Reyataz; ***Israel***: Reyataz; ***Ital.***: Reyataz; ***Jpn***: Reyataz; ***Malaysia***: Reyataz; ***Mex.***: Reyataz; ***Neth.***: Reyataz; ***Norw.***: Reyataz; ***NZ***: Reyataz; ***Pol.***: Reyataz; ***Port.***: Reyataz; ***Rus.***: Reyataz (Реатаз); ***S.Afr.***: Reyataz; ***Singapore***: Reyataz; ***Spain***: Reyataz; ***Swed.***: Reyataz; ***Switz.***: Reyataz; ***Thai.***: Reyataz; ***UK***: Reyataz; ***USA***: Reyataz.

Boceprevir *(USAN, rINN)*

Bocéprévir; Boceprevirum; SCH-503034; Боцепревир

(1*R*,2*S*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-{(2*S*)-2-[[(1,1-dimethylethyl)carbamoyl]amino]-3,3-dimethylbutanoyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide.

$C_{27}H_{45}N_5O_5$=519.7

CAS — 394730-60-0.

ATC — J05AE12.

ATC Vet — QJ05AE12.

UNII — 89BT58KELH.

Uses and Administration

Boceprevir is an oral peptidomimetic HCV-protease inhibitor effective against hepatitis C virus (HCV) protease NS3/4A. It is used in the treatment of chronic hepatitis C (p. 952.1) genotype 1 infection in adults with compensated liver disease, including cirrhosis. Boceprevir is given in an oral dose of 800 mg three times daily (once every 7 to 9 hours) with food in a combined regimen with peginterferon alfa and ribavirin.

Patients **without cirrhosis** who are previously untreated or who have failed previous treatment with peginterferon alfa and ribavirin should be given an initial 4 weeks of treatment with peginterferon alfa and ribavirin (bi-therapy). Boceprevir is then added to the regimen (tri-therapy), after which the course is determined by the patient's clinical situation and hepatitis C-RNA (HCV-RNA) response to therapy. UK- and US-licensed product information recommend the following approach:

Previously untreated patients

- where HCV-RNA is undetectable at weeks 8 and 24: complete tri-therapy until the end of week 28
- where HCV-RNA is detectable at week 8, but undetectable at week 24: continue tri-therapy to the end of week 36, then switch to bi-therapy until the end of week 48

Patients who have failed previous therapy with peginterferon alfa and ribavirin

- where HCV-RNA is undetectable at weeks 8 and 24: UK licensed product information advises tri-therapy up to the end of week 36, then bi-therapy until the end of week 48; US licensed product information advises tri-therapy up to the end of week 36
- where HCV-RNA is detectable at week 8, but undetectable at week 24: continue tri-therapy up to the end of week 36, then switch to bi-therapy until the end of week 48

Patients with **cirrhosis** should be given an initial 4 weeks of bi-therapy, followed by 44 weeks of tri-therapy. The duration of tri-therapy should not be less than 32 weeks; if tri-therapy is not tolerated, a switch to bi-therapy for the remaining 12 weeks can be considered.

In all patients, HCV-RNA levels ≥100 units/mL at week 12, or detectable HCV-RNA levels at week 24 are an indication of treatment futility, in which case tri-therapy should be abandoned.

References.

1. Kwo PY, *et al.* Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010; **376**: 705–16. Correction. *ibid.*; 1224.
2. Bacon BR, *et al.* HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207–17.
3. Poordad F, *et al.* SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195–206.

Adverse Effects

The addition of an HCV-protease inhibitor to a regimen of peginterferon alfa and ribavirin can result in significant additional toxicity, particularly dermatological, gastrointestinal, and haematological.

Adverse effects associated with the use of boceprevir with peginterferon alfa and ribavirin are wide ranging, but the most common adverse effects reported in clinical studies were anaemia, fatigue, headache, nausea, and taste disturbances. Other common effects that have been reported include increased incidence of infection, blood dyscrasias (including neutropenia, leucopenia, and thrombocytopenia), dry eyes or changes in vision, thyroid disturbances, reduced appetite, weight loss, dehydration, metabolic disturbances (such as hyperglycaemia, hypertriglyceridaemia, and hyperuricaemia), palpitations and changes in blood pressure, psychiatric disturbances, respiratory effects (including cough and dyspnoea), various CNS effects (such as dizziness, syncope, hypoaesthesia, or paraesthesia), tinnitus, gastrointestinal disturbances, effects on the skin (including alopecia, dry skin, pruritus, and rash), muscle and joint pain, frequent urination, erectile dysfunction, weakness, fever, chills, and malaise. Rare, but potentially serious adverse effects can include deafness, haemolysis, thyroid neoplasms, cardiac arrhythmias, thrombotic disorders (including deep-vein thrombosis and pulmonary embolism), pleural fibrosis and pleuritic pain, retinopathy, cerebral and retinal ischaemia, myocardial infarction, cholecystitis, pancreatitis, and gastritis.

Precautions

Boceprevir must not be used as monotherapy as there is a high likelihood of viral resistance developing. It is contra-indicated in patients with auto-immune hepatitis. Because boceprevir is given with peginterferon alfa and ribavirin, precautions with respect to the use of these medications must be observed (see p. 995.1 and p. 1011.2, respectively). Boceprevir-containing regimens generally increase the incidence and degree of anaemia and neutropenia compared with peginterferon alfa and ribavirin alone; complete blood counts should therefore be obtained before, and periodically throughout, treatment. Prompt evaluation and treatment of infections is necessary.

Boceprevir may have proarrhythmic effects and care is warranted in patients at risk for QT-interval prolongation.

Interactions

Boceprevir is a strong inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5; boceprevir in combination with peginterferon alfa and ribavirin is contra-indicated with drugs that are highly dependent on these enzymes for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. Although specific guidance may vary between licensing authorities, these drugs may include

- the alpha$_1$-adrenoceptor antagonist alfuzosin
- antimalarials (halofantrine and lumefantrine)
- antineoplastics (tyrosine kinase inhibitors)
- antipsychotics (pimozide)
- calcium-channel blockers (bepridil)
- the oral contraceptive hormone drospirenone
- ergot derivatives (dihydroergotamine, ergonovine, ergotamine, and methylergonovine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (lovastatin and simvastatin)

Owing to the potential for increased serum concentrations of phosphodiesterase type-5 inhibitor (such as sildenafil and tadalafil), boceprevir should also be avoided with these drugs when given at the doses needed for the treatment of pulmonary hypertension. Similarly, boceprevir may increase serum concentrations of inhaled budesonide, fluticasone, or salmeterol; combination with any of these is not recommended.

Boceprevir is partly metabolised by CYP3A4 and CYP3A5; as a result, drugs that induce or inhibit these enzymes might be expected to decrease or increase exposure to boceprevir. In particular, use with potent inducers of CYP3A4 and CYP3A5 (such as carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin, rifabutin, or St Johns wort) should be avoided.

Caution should be observed if boceprevir is to be given with drugs known to prolong the QT-interval (such as amiodarone, methadone, pentamidine, quinidine, and some antipsychotics).

Antiviral action

Boceprevir is a competitive inhibitor of the NS3/4A protease of hepatitis C virus (HCV) genotype 1, a protein involved in the post-translational processing of HCV polyproteins that is required for viral replication. The drug has no clinically significant activity against other HCV genotypes and must be used with peginterferon alfa and ribavirin to minimise the emergence of viral resistance.

Pharmacokinetics

Boceprevir is given as an equal mixture of two diastereomers, SCH534128 and SCH534129, only the first of which is pharmacologically active. It is well absorbed after oral administration and peak-plasma concentrations occur after a median 2 hours; in plasma, the diastereomer ratio changes to 2:1, favouring the active diastereomer SCH534128. Plasma concentrations increase in a less-than-dose-proportional manner, indicating that larger doses are not absorbed as well as smaller ones. Food enhances its absorption by up to 65% at a dose of 800 mg three times daily. Steady-state concentrations of boceprevir occur after about 1 day of regular dosing. It has a mean volume of distribution of about 772 litres and is about 75% bound to plasma proteins.

Boceprevir is metabolised through the aldo-ketoreductase (AKR)-mediated pathway to inactive ketone-reduced metabolites; to a lesser extent, it also undergoes oxidative metabolism via CYP3A4/5. It has a mean elimination half-life of about 3.4 hours, and is excreted mainly in the faeces as metabolites with less than 10% as unchanged drug. Renal excretion of boceprevir is relatively insignificant, and the drug is not removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Victrelis; ***Belg.***: Victrelis; ***Denm.***: Victrelis; ***Fr.***: Victrelis; ***Ger.***: Victrelis; ***Irl.***: Victrelis; ***Israel***: Victrelis; ***Neth.***: Victrelis; ***Norw.***: Victrelis; ***Singapore***: Victrelis; ***Spain***: Victrelis; ***Swed.***: Victrelis; ***Switz.***: Victrelis; ***UK***: Victrelis; ***USA***: Victrelis.

Brivudine (rINN)

Brivudin; Brivudina; Brivudinum; BVDU; Бривудин.
(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine.
$C_{11}H_{13}BrN_2O_5$=333.1
CAS — 69304-47-8.
ATC — J05AB15.
ATC Vet — QJ05AB15.
UNII — 2M3055079H.

Profile

Brivudine is a nucleoside analogue effective *in vitro* against herpes simplex virus type 1 and varicella-zoster virus; other viruses including herpes simplex virus type 2 have been reported to be sensitive, but only at relatively high concentrations. The activity appears to be due, at least in part, to selective phosphorylation of brivudine by viral deoxythymidine kinase in preference to cellular kinases. Cross-resistance is common between brivudine and aciclovir because of some similar features in their mode of action (see p. 966.1).

Brivudine is given orally in the treatment of herpes zoster (p. 956.2) in a dose of 125 mg daily for 7 days. It has also been given orally for herpes simplex infection and has been used topically.

Brivudine has been investigated for the treatment of pancreatic cancer (p. 712.1) and has been granted orphan drug status by the EMA for this indication. When given with other antineoplastic drugs it acts by blocking heat shock protein 27 (Hsp27) which is found in high amounts in pancreatic cancer cells and plays an important role in chemoresistance.

References.
1. Keam SJ, *et al.* Brivudin (bromovinyl deoxyuridine). *Drugs* 2004; 64: 2091–7.
2. Wassilew S. Collaborative Brivudin PHN Study Group. Brivudin compared with famciclovir in the treatment of herpes zoster: effects in acute disease and chronic pain in immunocompetent patients. A randomized, double-blind, multinational study. *J Eur Acad Dermatol Venereol* 2005; 19: 47–55.
3. Mottu A, *et al.* Acute hepatitis due to brivudin: a case report. *J Hepatol* 2009; 51: 967–9.
4. Fahrig R, *et al.* RP101 improves the efficacy of chemotherapy in pancreas carcinoma cell lines and pancreatic cancer patients. *Anticancer Drugs* 2006; 17: 1045–56.

Interactions. For reference to a fatality when brivudine was given with *capecitabine* see under Interactions, Antivirals, in Fluorouracil, p. 797.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zostydol; *Austria*: Mevir; Zostex; *Belg.*: Zerpex; Zonavir; *China*: Zostex (左伏); *Cz.*: Zostevir; *Ger.*: Zostex; *Gr.*: Brivir; Zostevir; *Ital.*: Brivirac; Zecovir; *Port.*: Bridic Zostex; *Spain*: Nervinex; *Switz.*: Brivex; *Turk.*: Zostex.

Cidofovir (BAN, USAN, rINN)

Cidofovirum; Cydofowir; GS-0504; GS-504; HPMPC; Sidofoviiri; Sidofovir; Цидофовир.
[[(*S*)-2-(4-Amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl) ethoxy]methyl]phosphonic acid; 1-[(*S*)-3-Hydroxy-2-(phosphonomethoxy)propyl]-cytosine.
$C_8H_{14}N_3O_6P$=279.2
CAS — 113852-37-2 (anhydrous cidofovir); 149394-66-1 (cidofovir dihydrate).
ATC — J05AB12.
ATC Vet — QJ05AB12.
UNII — JL713Q00N (cidofovir); 768M1V522C (anhydrous cidofovir).

Uses and Administration

Cidofovir is a nucleoside analogue that is active against herpesviruses. It is used in the treatment of CMV retinitis (p. 954.2) in patients with AIDS, and is being investigated for ocular herpes simplex and other viral infections.

In the treatment of CMV retinitis, cidofovir is given in a dose of 5 mg/kg by intravenous infusion over 1 hour once a week for 2 consecutive weeks, then once every 2 weeks for maintenance. Probenecid 2 g is given orally 3 hours before each dose of cidofovir and further 1-g doses of probenecid at 2 and 8 hours after completion of the infusion. To ensure adequate hydration, 1 litre of sodium chloride 0.9% is given by intravenous infusion over 1 to 2 hours immediately before each infusion of cidofovir; if the additional fluid load can be tolerated, a further 1 litre of sodium chloride 0.9% may be infused over 1 to 3 hours, starting at the same time as (or immediately after) the cidofovir infusion. For details of modified use of cidofovir in patients with renal impairment, see below.

Cidofovir has also been given experimentally by intravitreal injection but the commercially available formulation is unsuitable for use by this route and licensed product information advises against it (see Precautions, below).

An orally active prodrug of cidofovir known as cyclic-HPMPC (GS-930) is under investigation; a lipophilic analogue, 3-hexadecyloxy-1-propanol cidofovir (CMX-001) is also under investigation for its potential activity against a range of viruses including herpes viruses (such as CMV), BK virus, and smallpox. Cidofovir has been investigated for topical use.

Reviews.
1. Lea AP, Bryson HM. Cidofovir. *Drugs* 1996; 52: 225–30.
2. Kendle JB, Fan-Havard P. Cidofovir in the treatment of cytomegaloviral disease. *Ann Pharmacother* 1998; 32: 1181–92.
3. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. *Drugs* 1999; 58: 325–45.
4. De Clercq E. Cidofovir in the treatment of poxvirus infections. *Antiviral Res* 2002; 55: 1–13.
5. Snoeck R, De Clercq E. Role of cidofovir in the treatment of DNA virus infections, other than CMV infections, in immunocompromised patients. *Curr Opin Investig Drugs* 2002; 3: 1561–6.
6. Toro JR, *et al.* Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox. *Dermatol Clin* 2003; 21: 301–9.
7. Cha S, *et al.* Treatment of verruca vulgaris with topical cidofovir in an immunocompromised patient: a case report and review of the literature. *Transpl Infect Dis* 2005; 7: 158–61.
8. Soma MA, Albert DM. Cidofovir: to use or not to use? *Curr Opin Otolaryngol Head Neck Surg* 2008; 16: 86–90.
9. Donne AJ, *et al.* Scientific and clinical aspects of the use of cidofovir in recurrent respiratory papillomatosis. *Int J Pediatr Otorhinolaryngol* 2008; 72: 939–44.
10. Lamoth F, *et al.* Low-dose cidofovir for the treatment of polyomavirus-associated nephropathy: two case reports and review of the literature. *Antivir Ther* 2008; 13: 1001–9.
11. Coremans G, Snoeck R. Cidofovir: clinical experience and future perspectives on an acyclic nucleoside phosphonate analog of cytosine in the treatment of refractory and premalignant HPV-associated anal lesions. *Expert Opin Pharmacother* 2009; 10: 1343–52.
12. Moyo TK, *et al.* Review: use of cidofovir for the treatment of HIV-negative human herpes virus-8-associated primary effusion lymphoma. *Clin Adv Hematol Oncol* 2010; 8: 372–4.

Administration in renal impairment. Cidofovir is contra-indicated in patients with pre-existing renal impairment (serum creatinine more than 1.5 mg/dL, creatinine clearance of 55 mL/min or less, or urine protein of 100 mg/dL or more) and should be interrupted or stopped if serum creatinine increases by 500 micrograms/dL or more during therapy, or if significant proteinuria develops; in the USA, a reduction in the maintenance dose from 5 to 3 mg/kg intravenously is permitted for increases of serum creatinine of 300 to 400 micrograms/dL above baseline.

Viral infections. In addition to its use in CMV retinitis, systemic cidofovir has also been studied in herpes simplex infections,[1-4] progressive multifocal leukoencephalopathy,[5-9] BK polyomavirus-associated haemorrhagic cystitis,[4,10] and papillomavirus infections.[11] Topical formulations of cidofovir, in concentrations ranging from 0.3 to 5%, have also been used for the treatment of herpes simplex[12,13] and papillomavirus infections,[14-20] and molluscum contagiosum.[18,21,22]

See also reviews listed above.

1. Lalezari JP, *et al.* Treatment with intravenous (S)-1-(3-hydroxy-2-(phosphonylmethoxy)propyl]-cytosine of acyclovir-resistant mucocutaneous infection with herpes simplex virus in a patient with AIDS. *J Infect Dis* 1994; 170: 570–2.
2. Bryant P, *et al.* Successful treatment of foscarnet-resistant herpes simplex stomatitis with intravenous cidofovir in a child. *Pediatr Infect Dis J* 2001; 20: 1083–6.
3. Kopp T, *et al.* Successful treatment of an aciclovir-resistant herpes simplex type 2 infection with cidofovir in an AIDS patient. *Br J Dermatol* 2002; 147: 134–8.
4. Andrei G, *et al.* Dual infection with polyomavirus BK and acyclovir-resistant herpes simplex virus successfully treated with cidofovir in a bone marrow transplant recipient. *Transpl Infect Dis* 2007; 9: 126–31.
5. Segarra-Newnham M, Vodolo KM. Use of cidofovir in progressive multifocal leukoencephalopathy. *Ann Pharmacother* 2001; 35: 741–4.
6. Razonable RR, *et al.* Cidofovir treatment of progressive multifocal leukoencephalopathy in a patient receiving highly active antiretroviral therapy. *Mayo Clin Proc* 2001; 76: 1171–5.
7. Marra CM, *et al.* Adult AIDS Clinical Trials Group 363 Team. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002; 16: 1791–7.
8. Garvey L, *et al.* Progressive multifocal leukoencephalopathy: prolonged survival in patients treated with protease inhibitors and cidofovir: a case series. *AIDS* 2006; 20: 791–3.
9. Viallard JF, *et al.* Improvement of progressive multifocal leukoencephalopathy after cidofovir therapy in a patient with a destructive polyarthritis. *Infection* 2007; 35: 33–6.
10. Cesaro S, *et al.* Cidofovir for BK virus-associated hemorrhagic cystitis: a retrospective study. *Clin Infect Dis* 2009; 49: 233–40.
11. Kottke MD, Parker SRS. Intravenous cidofovir-induced resolution of disfiguring cutaneous human papillomavirus infection. *J Am Acad Dermatol* 2006; 55: 533–6.
12. Lalezari J, *et al.* A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis* 1997; 176: 892–8.
13. Sacks SL, *et al.* A multicenter phase I/II dose escalation study of single-dose cidofovir gel for treatment of recurrent genital herpes. *Antimicrob Agents Chemother* 1998; 42: 2996–9.
14. Snoeck R, *et al.* Treatment of anogenital papillomavirus infections with an acyclic nucleoside phosphonate analogue. *N Engl J Med* 1995; 333: 943–4.
15. Davis MDP, *et al.* Large plantar wart caused by human papillomavirus-16 and resolution by topical cidofovir therapy. *J Am Acad Dermatol* 2000; 43: 340–3.
16. Descamps V, *et al.* Topical cidofovir for bowenoid papulosis in an HIV-infected patient. *Br J Dermatol* 2001; 144: 642–3.
17. Snoeck R, *et al.* Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. *Clin Infect Dis* 2001; 33: 597–602.
18. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS: a pilot study. *J Eur Acad Dermatol Venereol* 2000; 14: 484–8.
19. Husak R, *et al.* Refractory human papillomavirus-associated oral warts treated topically with 1-3% cidofovir solutions in human immunodeficiency virus type 1-infected patients. *Br J Dermatol* 2005; 152: 590–1.
20. Field S, *et al.* The treatment of viral warts with topical cidofovir 1%: our experience of seven paediatric patients. *Br J Dermatol* 2009; 160: 223–4.
21. Davies EG, *et al.* Topical cidofovir for severe molluscum contagiosum. *Lancet* 1999; 353: 2042.
22. Toro JR, *et al.* Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. *Arch Dermatol* 2000; 136: 983–5.

Adverse Effects

The most serious dose-limiting adverse effect of cidofovir is nephrotoxicity, the incidence and severity of which can be reduced by use with probenecid and by ensuring adequate hydration. Accumulation of cidofovir in the renal tubules can also be prevented by using an intermittent dosing schedule (see the licensed doses in Uses and Administration above). There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Cases of nephrotoxicity have also been reported after off-label use of topical applications (creams or ointments) of cidofovir. Ocular toxicity and neutropenia have also been reported after use for off-label indications or by unlicensed routes of administration. Low plasma-bicarbonate concentrations and metabolic acidosis, sometimes associated with proximal tubule injury and renal wasting syndrome (including Fanconi's syndrome) or with liver dysfunction and pancreatitis, have been reported. Reversible neutropenia has also occurred. Other adverse effects include diarrhoea, headache, nausea and vomiting, fever, chills, asthenia, rash, dyspnoea, alopecia, and ocular hypotony (decreased intraocular pressure). Iritis or uveitis has been reported.

Cidofovir is carcinogenic and embryotoxic in *animals* and may have the potential to cause male infertility (see Precautions, below).

Effects on the eyes. Ocular adverse effects associated with intravenous use of cidofovir include iritis,[1] uveitis,[2-4] and ocular hypotony.[4] While development of ocular hypotony is considered to warrant withdrawal of cidofovir,[2] uveitis or iritis alone may respond to topical corticosteroids and cycloplegics thus allowing antiviral therapy to be continued; cidofovir must be stopped if there is no response or worsening of symptoms.

1. Tseng AL, *et al.* Iritis associated with intravenous cidofovir. *Ann Pharmacother* 1999; 33: 167–71.
2. Ambati J, *et al.* Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. *Br J Ophthalmol* 1999; 83: 1153–8.
3. Rougier M-B, *et al.* Uvéite antérieure et cidofovir. *J Fr Ophtalmol* 2001; 24: 491–5.
4. Rapp P, *et al.* Uvéite bilatérale et hypotonie définitive due au cidofovir intraveineux: à propos d'un cas. *J Fr Ophtalmol* 2003; 26: 717–19.

Effects on the kidneys. Dose-related nephrotoxicity is the most severe adverse effect of cidofovir and marked proteinuria has been reported in up to 50% of patients. There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Fanconi's syndrome associated with renal tubular damage has been reported in 2% of patients and, in one such patient, occurred on the third injection of cidofovir and resulted in irreversible renal impairment.[1] Reversible renal impairment with persisting Fanconi syndrome was reported in another.[2] A case of nephrogenic diabetes insipidus without premonitory laboratory abnormalities has also been reported in a patient given cidofovir.[3]

1. Vitucoq D, *et al.* Fanconi syndrome associated with cidofovir therapy. *Antimicrob Agents Chemother* 1997; 41: 1846.
2. Kazory A, *et al.* Simultaneous development of Fanconi syndrome and acute renal failure associated with cidofovir. *J Antimicrob Chemother* 2007; 60: 193–4.
3. Schliefer K, *et al.* Nephrogenic diabetes insipidus in a patient taking cidofovir. *Lancet* 1997; 350: 413–14. Correction. *ibid.*: 1558.

Precautions

Cidofovir is contra-indicated in patients with renal impairment. Renal function should be measured before each dose. In the UK it is recommended that treatment should be interrupted or stopped if renal function deteriorates, but in the USA reduction of the dosage is permitted for increases in serum creatinine up to 300 to 400 micrograms/dL above baseline. Patients should receive oral probenecid and intravenous hydration with each dose of cidofovir; if probenecid cannot be used due to clinically significant hypersensitivity (to it or another sulfonamide drug), the use of cidofovir is also contra-indicated. Cidofovir should not be given with tenofovir disoproxil fumarate due

to the increased risk of Fanconi syndrome. Neutrophil counts should also be monitored and regular ophthalmological follow-up is recommended. Patients with diabetes mellitus are at increased risk of ocular hypotony.

Cidofovir is carcinogenic and embryotoxic in *animals*. Cidofovir should not be given during pregnancy and both sexes should use effective methods of contraception during treatment; in addition, effective contraception should be used, for 1 month by women and for 3 months by men, after the end of treatment. There is also a possibility that cidofovir may cause male infertility.

Cidofovir should be given intravenously only; direct intra-ocular injection has been associated with significant ocular hypotony and visual impairment and is contra-indicated.

Interactions

Additive nephrotoxicity may occur if cidofovir is used with other nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, vancomycin, or NSAIDs. Potentially nephrotoxic drugs should be stopped at least 7 days before starting cidofovir. Probenecid, which is given with cidofovir, may alter the clearance of other drugs (see Interactions under Probenecid, p. 608.2). Renal excretion of cidofovir may possibly also be affected by other drugs that are excreted by glomerular filtration and/or tubular secretion.

Patients with CMV retinitis are at increased risk of adverse inflammatory effects if cidofovir is given within 2 to 4 weeks of intravitreal fomivirsen.

Antiviral Action

Cidofovir undergoes intracellular phosphorylation by cellular kinases to the antiviral metabolite, cidofovir diphosphate, which acts as a competitive inhibitor of viral DNA polymerase. It is active against a range of herpesviruses including CMV, and, since its activity is not reliant on viral enzymes, may retain activity against some aciclovir- and foscarnet-resistant viruses. Cross-resistance with ganciclovir is common.

References.
1. Cherrington JM, *et al.* In vitro antiviral susceptibilities of isolates from cytomegalovirus retinitis patients receiving first- or second-line cidofovir therapy: relationship to clinical outcome. *J Infect Dis* 1998; **178**: 1821–5.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42**: 2240–4.

Pharmacokinetics

After intravenous doses of cidofovir, serum concentrations decline with a reported terminal half-life of about 2.2 hours (the intracellular half-life of the active diphosphate may be up to 65 hours). Cidofovir is eliminated mainly by renal excretion, both by glomerular filtration and tubular secretion. About 80 to 100% of a dose is recovered unchanged from the urine within 24 hours. Use with probenecid may reduce the excretion of cidofovir to some extent by blocking tubular secretion, although 70 to 85% has still been reported to be excreted unchanged in the urine within 24 hours.

References.
1. Cundy KC. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovir and adefovir. *Clin Pharmacokinet* 1999; **36**: 127–43.
2. Brody SR, *et al.* Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis. *Clin Pharmacol Ther* 1999; **65**: 21–8.
3. Wolf DL, *et al.* Pharmacokinetics and renal effects of cidofovir with a reduced dose of probenecid in HIV-infected patients with cytomegalovirus retinitis. *J Clin Pharmacol* 2003; **43**: 43–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vistide; ***Austria***: Vistide; ***Belg.***: Vistide; ***Cz.***: Vistide; ***Denm.***: Vistide; ***Fr.***: Vistide; ***Ger.***: Vistide; ***Gr.***: Vistide; ***Irl.***: Vistide; ***Ital.***: Vistide; ***Neth.***: Vistide; ***Pol.***: Vistide; ***Port.***: Vistide; ***Spain***: Vistide; ***Swed.***: Vistide; ***Switz.***: Vistide; ***UK***: Vistide; ***USA***: Vistide.

Daclatasvir *(USAN, pINN)*

BMS-790052; Daclatasvirum; Даклатасвир.

Dimethyl *N,N'*-(biphenyl-4,4'-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-1-(1-methylethyl)-2-oxoethane-2,1-diyl]})dicarbamate.

$C_{40}H_{50}N_8O_6$=738.9

CAS — 1009119-64-5.

UNII — LI2427F9CI.

Profile

Daclatasvir is an oral replication complex inhibitor of hepatitis C virus (HCV) protein NS5A. It is used, combined with other antivirals, for the treatment of chronic hepatitis C (p. 952.1) infection; it has broad genotypic coverage. An oral dose of daclatasvir 60 mg once daily, given with sofosbuvir (p. 1015.2), has been used in clinical studies.

References.
1. Lee C. Daclatasvir: potential role in hepatitis C. *Drug Des Devel Ther* 2013; **7**: 1223–33.
2. Herbst DA, Reddy KR. NS5A inhibitor, daclatasvir, for the treatment of chronic hepatitis C virus infection. *Expert Opin Invest Drugs* 2013; **22**: 1337–46.

Darunavir *(BAN, USAN, rINN)*

Darunavirum; TMC-114; UIC-94017; Дарунавир.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-(*N*^{1}-isobutylsulfanilamido)propyl]carbamate.

$C_{27}H_{37}N_3O_7S$=547.7

CAS — 206361-99-1.

ATC — J05AE10.

ATC Vet — QJ05AE10.

UNII — YO603Y8113.

Darunavir Ethanolate *(BANM, rINNM)*

Darunavir monoethanolate.

$C_{27}H_{37}N_3O_7S,C_2H_5OH$=593.7

ATC — J05AE10.

ATC Vet — QJ05AE10.

UNII — 33O78XF0BW.

Uses and Administration

Darunavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when darunavir is used alone, and it is therefore used with other antiretrovirals.

Darunavir is boosted with low-dose ritonavir, which acts as a pharmacokinetic enhancer. It is given orally as the ethanolate, but doses are expressed in terms of the base; 325 mg of darunavir ethanolate is equivalent to about 300 mg of darunavir.

In treatment-naive patients, the recommended dose of darunavir is 800 mg (with ritonavir 100 mg) once daily with food. In treatment-experienced patients doses are generally chosen based on the degree of darunavir resistance seen via genotypic testing; however where testing is not feasible, a dose of 600 mg (with ritonavir 100 mg) twice daily is recommended.

For details of doses in children, see below.

References.
1. Clotet B, *et al.* Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369**: 1169–78.
2. Busse KH, Penzak SR. Darunavir: a second-generation protease inhibitor. *Am J Health-Syst Pharm* 2007; **64**: 1593–602.
3. McKeage K, *et al.* Darunavir: a review of its use in the management of HIV infection in adults. *Drugs* 2009; **69**: 477–503.
4. Fullerton DS, *et al.* Pharmacoeconomics of darunavir. *Expert Rev Pharmacoecon Outcomes Res* 2011; **11**: 27–39.

Administration in children. Ritonavir-boosted darunavir may be used, with other antiretroviral drugs, for the treatment of HIV infection in children 6 years of age and older and weighing at least 20 kg. In the UK, it is further recommended that use of darunavir be reserved for treatment-experienced children only. The following oral doses are recommended, based on body-weight, and should not exceed the recommended adult dose for treatment-experienced patients (see above):

- 20 to less than 30 kg: darunavir 375 mg (with ritonavir 50 mg) twice daily
- 30 to less than 40 kg: darunavir 450 mg (with ritonavir 60 mg) twice daily
- 40 kg and over: darunavir 600 mg (with ritonavir 100 mg) twice daily

Further references to use in children.

1. Blanche S, *et al.* Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS* 2009; **23**: 2005–13.
2. Neely M, Kovacs A. Managing treatment-experienced pediatric and adolescent HIV patients: role of darunavir. *Ther Clin Risk Manag* 2009; **5**: 595–615.
3. McKeage K, Scott LJ. Darunavir: in treatment-experienced pediatric patients with HIV-1 infection. *Paediatr Drugs* 2010; **12**: 123–31.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing darunavir are gastrointestinal disturbances (abdominal pain, diarrhoea, nausea, and vomiting), nasopharyngitis, and hypertriglyceridaemia. Rashes (usually of mild to moderate severity) are seen in about 5 to 10% of patients, typically occurring within the first 4 weeks of treatment and resolving without stopping treatment. Severe rashes, including erythema multiforme and Stevens-Johnson syndrome, have occurred more rarely; treatment should be stopped if severe rash develops.

Other reported adverse effects are asthenia, dizziness, fatigue, headache, and insomnia. Less frequently reported adverse effects include folliculitis, myocardial infarction, osteopenia, osteoporosis, polyuria, somnolence, tachycardia, transient ischaemic attacks, and vertigo. Cases of drug-induced hepatitis, including fatalities, have been reported. Abnormal liver and pancreatic function tests, anaemia, neutropenia, and thrombocytopenia have also occurred.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including darunavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including darunavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Patients should undergo liver function tests before starting and during treatment with darunavir. It should not be used in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution (and liver enzymes values monitored), in those with mild to moderate impairment (Child-Pugh A or B) and those with chronic hepatitis B or C co-infection. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. All patients should be instructed to seek medical advice if symptoms suggestive of new or worsening hepatotoxicity occur.

Darunavir contains a sulfonamide moiety and should be used with caution in patients with known sulfonamide hypersensitivity, although its cross-sensitivity potential with sulfonamide drugs is unknown. (For discussion of cross-reactivity in sulfonamides and *sulfa drugs* see Hypersensitivity under Sulfamethoxazole, p. 365.3.) Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. An association with erythema multiforme and Stevens-Johnson syndrome has been reported and treatment should be stopped in patients who develop severe rashes.

Interactions

Darunavir inhibits, and is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It may affect the clearance of other drugs metabolised by this enzyme, potentially resulting in increased plasma concentrations and toxicity.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted darunavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- antiarrhythmics (amiodarone, bepridil, quinidine, and systemic lidocaine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide and sertindole)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated. Owing to the potential for increased serum concentrations of sildenafil, ritonavir-boosted darunavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir-boosted darunavir may increase serum concentrations of inhaled fluticasone and salmeterol and combination with either is not recommended. Ritonavir-boosted lopinavir, rifampicin, saquinavir, antiepileptics (phenobarbital and phenytoin), and St John's wort decrease the concentration of darunavir; use

with darunavir is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Darunavir is a selective inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance may develop between some HIV-protease inhibitors, but mechanisms of resistance to darunavir may differ from those to other drugs of the class.

Pharmacokinetics

Darunavir is rapidly absorbed after oral doses, resulting in a bioavailability of 82% when taken with recommended doses of ritonavir; food increases the bioavailability. Peak plasma concentrations occur within 2.5 to 4 hours. Darunavir is about 95% bound to plasma proteins. It is metabolised by oxidation by the cytochrome P450 system (mainly the isoenzyme CYP3A4), with at least 3 metabolites showing some antiretroviral activity. About 80% of a dose is excreted in the faeces, with 41.2% of this as unchanged drug; 14% is excreted in the urine, with 7.7% being unchanged drug. The mean terminal elimination half-life of darunavir is about 15 hours.

Reviews.

1. Rittweger M, Arasteh K. Clinical pharmacokinetics of darunavir. *Clin Pharmacokinet* 2007; 46: 739–56.
2. Vermeir M, *et al.* Absorption, metabolism, and excretion of darunavir, a new protease inhibitor, administered alone and with low-dose ritonavir in healthy subjects. *Drug Metab Dispos* 2009; 37: 809–20.
3. Yilmaz A, *et al.* Darunavir concentrations in cerebrospinal fluid and blood in HIV-1-infected individuals. *AIDS Res Hum Retroviruses* 2009; 25: 457–61.
4. Giguère P, *et al.* Pharmacokinetics of darunavir, efavirenz and raltegravir in an HIV-infected patient on haemodialysis. *AIDS* 2009; 23: 760–2.
5. Ripamonti D, *et al.* Transplacental passage of ritonavir-boosted darunavir in two pregnant women. *Int J STD AIDS* 2009; 20: 215–16.
6. Sekar V, *et al.* Pharmacokinetics of multiple-dose darunavir in combination with low-dose ritonavir in individuals with mild-to-moderate hepatic impairment. *Clin Pharmacokinet* 2010; 49: 343–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Prezista; ***Austral.***: Prezista; ***Austria***: Prezista; ***Belg.***: Prezista; ***Braz.***: Prezista; ***Canad.***: Prezista; ***Chile***: Prezista; ***China***: Prezista (紫力); ***Cz.***: Prezista; ***Denm.***: Prezista; ***Fr.***: Prezista; ***Ger.***: Prezista; ***Gr.***: Prezista; ***Hung.***: Prezista; ***Irl.***: Prezista; ***Israel***: Prezista; ***Ital.***: Prezista; ***Malaysia***: Prezista; ***Neth.***: Prezista; ***Norw.***: Prezista; ***NZ***: Prezista; ***Pol.***: Prezista; ***Port.***: Prezista; ***Rus.***: Prezista (Презиста); ***Singapore***: Prezista; ***Spain***: Prezista; ***Swed.***: Prezista; ***Switz.***: Prezista; ***Thai.***: Prezista; ***Turk.***: Prezista; ***UK***: Prezista; ***USA***: Prezista.

Delavirdine Mesilate *(rINNM)*

Delavirdina, mesilato de; Délavirdine, Mésilate de; Delavirdine Mesylate (USAN); Delavirdini Mesilas; Mesilato de delavirdina; U-90152S; Делавирдина Мезилат.

1-[3-(Isopropylamino)-2-pyridyl]-4-[(5-methanesulfonamidoindol-2-yl)carbonyl]-piperazine monomethanesulfonate.

$C_{22}H_{28}N_6O_3S.CH_4O_3S$=552.7

CAS — 136817-59-9 (delavirdine); 147221-93-0 (delavirdine mesilate).

ATC — J05AG02.

ATC Vet — QJ05AG02.

UNII — 421105KRQE.

Uses and Administration

Delavirdine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Viral resistance emerges rapidly when delavirdine is used alone, and it is therefore used with other antiretrovirals for combination therapy of HIV infection and AIDS (p. 957.2).

Delavirdine is given orally as the mesilate in a usual dose of 400 mg three times daily. Some tablet formulations may be dispersed in water before use in order to increase bioavailability (see below).

Reviews.

1. Scott LJ, Perry CM. Delavirdine: a review of its use in HIV infection. *Drugs* 2000; 60: 1411–44.

Adverse Effects

Adverse effects associated with antiretroviral regimens containing delavirdine are mostly mild to moderate. The most common adverse effect of delavirdine is rash, (usually diffuse, maculopapular, erythematous, and often pruritic), generally appearing within the first 3 weeks of starting therapy and resolving in 3 to 14 days. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse effects of moderate to severe intensity include generalised abdominal pain, asthenia, fatigue, fever, flu syndrome, headache, and localised pain. Other reported adverse effects include gastrointestinal disturbances (diarrhoea, nausea, vomiting), increased liver enzyme values, anxiety, depressive symptoms, insomnia, and respiratory effects (bronchitis, cough, pharyngitis, sinusitis, and upper respiratory-tract infections). Liver failure, haemolytic anaemia, rhabdomyolysis, and acute renal failure have been reported during postmarketing use.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including delavirdine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including delavirdine.

Precautions

Delavirdine should be stopped if a severe rash develops or if a rash is accompanied by fever, blistering, oral lesions, conjunctivitis, swelling, or muscle or joint aches. Delavirdine should be used with caution in patients with hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies delavirdine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Delavirdine has been shown to be teratogenic in *animals*. Clinical studies and postmarketing data have identified 10 infants born to mothers who took delavirdine during pregnancy. Eight of the infants were born healthy, 1 infant was born HIV-positive but had no congenital abnormalities, and 1 infant was born prematurely with a small muscular ventricular septal defect that spontaneously resolved.

Interactions

Delavirdine is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. Consequently it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of delavirdine. The absorption of delavirdine is reduced by drugs that raise gastric pH such as antacids, histamine H_2-antagonists, and proton pump inhibitors.

Delavirdine is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life threatening events. These drugs include antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (alprazolam, midazolam, triazolam). The antiepileptics carbamazepine, phenytoin, and phenobarbital, the antimycobacterials rifabutin and rifampicin, and St John's wort decrease the concentration of delavirdine; use with the antiretroviral is not recommended due to the possible loss of antiviral activity and development of resistance.

Antibacterials. Plasma concentrations of *dapsone* and *rifabutin* may be increased by delavirdine; *rifabutin* and *rifampicin*[1] may reduce delavirdine plasma concentrations and the use of either of these drugs with delavirdine is not recommended. For further information see under Rifampicin, p. 353.2 and Rifabutin, p. 350.1.

1. Borin MT, *et al.* Pharmacokinetic study of the interaction between rifampin and delavirdine mesylate. *Clin Pharmacol Ther* 1997; 61: 544–53.

Antivirals. Use of delavirdine with buffered *didanosine* may result in reduced plasma concentrations of both drugs[1] and they should be given at least 1 hour apart.

Plasma concentrations of *HIV-protease inhibitors* may be increased by delavirdine (see Antivirals, under Interactions of Indinavir, p. 988.1). Doses of indinavir should therefore be reduced; with saquinavir, liver function should be monitored.

In return, *nelfinavir*, and *fosamprenavir* have been reported to decrease plasma concentrations of delavirdine; UK licensed product information for nelfinavir advises that use with delavirdine is not recommended, while US licensed product information for fosamprenavir contra-indicates use with delavirdine due to possible loss of virological response with development of delavirdine resistance.

1. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; 41: 169–74.

Antiviral Action

Delavirdine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to delavirdine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Delavirdine is rapidly absorbed after oral doses and peak plasma concentrations occur after about 1 hour. The bioavailability of delavirdine tablets is about 85% of that from an oral solution after a single dose. The bioavailability of the 100-mg tablet can be increased by about 20% by dissolving it in water before use; the 200-mg tablets do not readily disperse in water and should be swallowed intact. Delavirdine is about 98% bound to plasma proteins. It is extensively metabolised by hepatic microsomal enzymes, mainly by the cytochrome P450 isoenzyme CYP3A4 (although CYP2D6 may play some role), to several inactive metabolites. The plasma half-life after usual dosage is about 5.8 hours and ranges from 2 to 11 hours. Delavirdine is excreted as metabolites in the urine and faeces. Less than 5% is excreted in the urine unchanged.

Reviews.

1. Voorman RL, *et al.* Metabolism of delavirdine, a human immunodeficiency virus type-1 reverse transcriptase inhibitor, by microsomal cytochrome P450 in humans, rats, and other species: probable involvement of CYP2D6 and CYP3A. *Drug Metab Dispos* 1998; 26: 631–9.
2. Tran JQ, *et al.* Delavirdine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2001; 40: 207–26.
3. Shelton MJ, *et al.* Pharmacokinetics of ritonavir and delavirdine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2003; 47: 1694–9.
4. Smith PF, *et al.* Population pharmacokinetics of delavirdine and N-delavirdine in HIV-infected individuals. *Clin Pharmacokinet* 2005; 44: 99–109.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Rescriptor; ***Canad.***: Rescriptor; ***USA***: Rescriptor.

Denotivir *(pINN)*

Dénotivir; Denotivirum; Денотивир.

5-Benzamido-4'-chloro-3-methyl-4-isothiazolecarboxanilide.

$C_{18}H_{14}ClN_3O_2S$=371.8

CAS — 51287-57-1.

UNII — W6565I100W.

Profile

Denotivir has antiviral, antibacterial, and anti-inflammatory properties. It is used topically as a 3% cream in the treatment of herpes virus infections and in other skin disorders complicated by bacterial infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Polvir†; Vratizolin; ***Ukr.***: Vratizolin (Вратизолин).

Didanosine *(BAN, USAN, rINN)*

BMY-40900; DDI; ddIno; Didanocin; Didanosiini; Didanosin; Didanosina; Didanosinum; Didanozin; Didanozinas; Dideoxyinosine; Didesoxinosina; NSC-612049; Диданозин.

2',3'-Dideoxyinosine.

$C_{10}H_{12}N_4O_3$=236.2

CAS — 69655-05-6.

ATC — J05AF02.

ATC Vet — QJ05AF02.

UNII — K3GDH6OH08.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Didanosine). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in dimethyl sulfoxide.

USP 36: (Didanosine). A white to off-white crystalline powder. Practically insoluble or insoluble in acetone and in methyl alcohol; very soluble in dimethyl sulfoxide. Store at

a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Didanosine is a nucleoside reverse transcriptase inhibitor structurally related to inosine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when didanosine is used alone, and it is therefore used with other antiretrovirals.

Didanosine is given orally, usually as buffered chewable/dispersible tablets or enteric-coated capsules. Doses should be taken at least 30 minutes before, or 2 hours after, a meal. The total daily dose may be given as either a single dose or as two divided doses, the choice being dependent upon both the formulation and the strength used. For those weighing more than 60 kg the recommended dose is 400 mg daily and for those under 60 kg, 250 mg daily is given. In the USA, it is recommended that enteric-coated capsules (*Videx EC, BMS*) be given in a single, daily dose of 200 mg to those weighing less than 25 kg.

For details of doses in children, see below.

Doses of didanosine may need to be amended when given with some other antiretrovirals. For further details see under Interactions, below.

Dosage reduction may be necessary in patients with renal (see below) or hepatic impairment, although no specific dose reductions are recommended in patients with hepatic impairment and close monitoring is required.

Reviews.

1. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection. *Drugs* 1999; 58: 1099–1135.
2. Moreno S, *et al.* Didanosine enteric-coated capsule: current role in patients with HIV-1 infection. *Drugs* 2007; 67: 1441–62.

Administration in children. For the treatment of HIV infection in children, didanosine is given daily with other antiretroviral drugs; doses are taken orally on an empty stomach.

In the USA an oral solution or enteric-coated tablet are available for use:

- the oral solution may be given to children from 2 weeks of age in the following doses based on age, and body-surface:
  - those between 2 weeks and 8 months of age: 100 mg/m^2 twice daily
  - those over 8 months of age: 120 mg/m^2 twice daily
- enteric-coated capsules may be given orally to children weighing at least 20 kg in the following doses based on body-weight:
  - 20 to less than 25 kg: 200 mg once daily
  - 25 to less than 60 kg: 250 mg once daily
  - 60 kg or more: 400 mg once daily

In the UK chewable or dispersible tablets or enteric-coated capsules are available for use; doses are based on body-surface:

- the chewable or dispersible tablets may be given orally to children older than 3 months of age, as either a single dose or as two divided doses, in a dose of 240 mg/m^2 daily *or* 180 mg/m^2 daily if given with zidovudine
- enteric-coated capsules may be given orally to children older than 6 years of age in a dose of 240 mg/m^2 daily *or* 180 mg/m^2 daily if given with zidovudine

Alternatively, the *BNFC* gives the following doses:

- 1 to 8 months of age: 50 to 100 mg/m^2 twice daily
- over 8 months of age: 180 to 240 mg/m^2 once daily to a maximum of 400 mg daily

Doses for children should not exceed those recommended for adults (see Uses and Administration, above).

Administration in renal impairment. Dosage of didanosine should be reduced in patients with renal impairment. The following oral doses are recommended based on the patient's weight and creatinine clearance (CC):

Adults weighing 60 kg or more:

- CC 60 mL/minute or more: usual adult doses
- CC 30 to 59 mL/minute: 200 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 150 mg once daily
- CC less than 10 mL/minute: 100 mg once daily

Adults less than 60 kg:

- CC 60 mL/minute or more: usual adult doses
- CC 30 to 59 mL/minute: 150 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 100 mg once daily
- CC less than 10 mL/minute: 75 mg once daily

For patients requiring intermittent haemodialysis or continuous ambulatory peritoneal dialysis, dosing recommendations for CC less than 10 mL/min may be used; doses should preferably be given after the dialysis run.

Adverse Effects

The most common serious adverse effects of didanosine are peripheral neuropathy and potentially fatal pancreatitis. Other commonly reported adverse effects include abdominal pain, diarrhoea, fatigue, headache, nausea, rash, and vomiting. Abnormal liver function tests may occur and hepatitis or fatal hepatic failure has been reported rarely; fatalities were reported most often in patients taking didanosine with stavudine and hydroxycarbamide. Non-cirrhotic portal hypertension, including cases resulting in liver transplantation or death, has also occurred. Retinal and optic-nerve changes have been reported in children, particularly in those taking higher than recommended doses; retinal depigmentation has been reported in adult patients. Other adverse effects include alopecia, anaemia, asthenia, dry mouth, fever, flatulence, parotid gland enlargement, leucopenia, hypersensitivity reactions including anaphylaxis, hyperuricaemia, and thrombocytopenia. Lactic acidosis usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs; it has sometimes been fatal, and generally occurs after some months of treatment.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including didanosine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including didanosine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the blood. In general, haematological abnormalities are less common in patients taking didanosine than in those taking zidovudine. However, there have been reports of thrombocytopenia associated with didanosine.[1-3]

1. Butler KM, *et al.* Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med* 1991; 324: 137–44.
2. Lor E, Liu YQ. Didanosine-associated eosinophilia with acute *thrombocytopenia*. *Ann Pharmacother* 1993; 27: 23–5.
3. Herranz P, *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; 344: 680.

Effects on the eyes. Retinal lesions with atrophy of the retinal pigment epithelium at the periphery of the retina were reported in 4 children receiving didanosine doses of 270 to 540 mg/m^2 daily.[1]

1. Whitcup SM, *et al.* Retinal lesions in children treated with dideoxyinosine. *N Engl J Med* 1992; 326: 1226–7.

Effects on the heart. For the possible risk of myocardial infarction in patients taking didanosine, see Effects on the Heart under Adverse Effects of Zidovudine, p. 1025.2.

Effects on the liver. Fatal fulminant hepatic failure was reported[1] in a patient receiving didanosine. A further 14 cases had been noted by the manufacturer, and elevated liver enzymes have been recorded during clinical studies.[2-5]

Potentially fatal non-cirrhotic portal hypertension (NCPH) has been reported in some HIV-infected individuals. In a nested, case-control study including 15 patients with NCPH and 75 matched control subjects, prolonged exposure to didanosine was found to be the only independent risk factor for NCPH in patients with HIV.[6]

1. Lai KK, *et al.* Fulminant hepatic failure associated with 2',3'-dideoxyinosine (ddI). *Ann Intern Med* 1991; 115: 283–4.
2. Dolin R, *et al.* Zidovudine compared with didanosine in patients with advanced HIV type 1 infection and little or no experience with zidovudine. *Arch Intern Med* 1995; 155: 961–74.
3. Jablonowski H, *et al.* A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; 9: 463–9.
4. Alpha International Coordinating Committee. The Alpha trial: European/Australian randomized double-blind trial of two doses of didanosine in zidovudine-intolerant patients with symptomatic HIV disease. *AIDS* 1996; 10: 867–80.
5. Gatell JM, *et al.* Switching from *zidovudine* to didanosine in patients with symptomatic HIV infection and disease progression. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; 12: 249–58.
6. Kovari H, *et al.* Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis* 2009; 49: 626–35.

Effects on mental state. Recurrent mania associated with didanosine treatment has been reported in a patient.[1]

1. Brouillette MJ, *et al.* Didanosine-induced mania in HIV infection. *Am J Psychiatry* 1994; 151: 1839–40.

Effects on the mouth. Xerostomia (dry mouth) may be a troublesome effect in patients receiving didanosine.[1,2]

1. Dodd CL, *et al.* Xerostomia associated with didanosine. *Lancet* 1992; 340: 790.
2. Valentine C, *et al.* Xerostomia associated with didanosine. *Lancet* 1992; 340: 1542.

Effects on the pancreas. Pancreatitis is recognised as being the most serious adverse effect of didanosine and can be fatal.[1-3] It appears to be dose-related, occurring in up to 13% of patients receiving 750 mg of didanosine daily.[2,4] Pancreatitis can resolve if didanosine is withdrawn[5] and cautious reintroduction of didanosine has been possible in some patients.[6] Raised amylase concentrations[5] and glucose intolerance have been reported in patients who subsequently developed pancreatitis.

1. Bouvet E, *et al.* Fatal case of 2',3'-dideoxyinosine-associated pancreatitis. *Lancet* 1990; 336: 1515.
2. Kahn JO, *et al.* A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *N Engl J Med* 1992; 327: 581–7.
3. Dolin R, *et al.* Zidovudine compared with didanosine in patients with advanced HIV-type 1 infection and little or no previous experience with zidovudine. *Arch Intern Med* 1995; 155: 961–74.
4. Jablonowski H, *et al.* A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; 9: 463–9.
5. Nguyen B-Y, *et al.* Five-year follow-up of a phase I study of didanosine in patients with advanced human immunodeficiency virus infection. *J Infect Dis* 1995; 171: 1180–9.
6. Butler KM, *et al.* Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics* 1993; 91: 747–51.

Effects on the skin. Didanosine has been implicated in a case of Stevens-Johnson syndrome[1] and of cutaneous vasculitis.[2]

1. Parneix-Spake A, *et al.* Didanosine as probable cause of Stevens-Johnson syndrome. *Lancet* 1992; 340: 857–8.
2. Herranz P, *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; 344: 680.

Precautions

Didanosine should be used with extreme caution in patients with a history of pancreatitis and those with increased triglyceride concentrations should be observed carefully for signs of pancreatitis and treatment with didanosine interrupted in all patients with signs and symptoms of possible pancreatitis, until it has been excluded. Alternative treatment regimens should also be considered in patients who develop symptoms of peripheral neuropathy. Use with other drugs likely to cause pancreatitis or peripheral neuropathy (see Interactions, below) should preferably be avoided; treatment with didanosine should be suspended if possible when use of such drugs is essential.

Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. However, cases of non-cirrhotic portal hypertension (some leading to liver transplantation or death) have also been reported in patients with no evidence of viral hepatitis. Didanosine should be given with caution to patients with hepatomegaly or other risk factors for liver disease and patients with hepatic impairment. Regular checks of liver function are recommended. If liver enzymes increase to more than 5 times the upper limit of normal during treatment then didanosine should be stopped. Patients should also be monitored for early signs of portal hypertension (including thrombocytopenia or splenomegaly). Didanosine should be stopped in patients with evidence of portal hypertension. Treatment with didanosine may be associated with lactic acidosis and should also be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, steatosis, or metabolic or lactic acidosis of unknown aetiology. Dosage reduction may be necessary in renal impairment.

To monitor for retinal or optic nerve changes, ophthalmic examination (including visual acuity, colour vision, and dilated fundus examination) should be considered annually in patients taking didanosine, as well as when any changes in vision are reported. didanosine withdrawn if they occur. Monitoring should also be considered in adults.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies didanosine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Use of didanosine with other drugs known to cause pancreatitis (for example intravenous pentamidine) or with drugs that may cause peripheral neuropathy (for example metronidazole, isoniazid, and vincristine) should be avoided. If co-administration is unavoidable, patients should be monitored carefully for these adverse effects.

An increase in the area under the plasma concentration-time curve for didanosine has been reported when allopurinol or other xanthine oxidase inhibitors are given concurrently; because of the risk of toxicity, use of didanosine with allopurinol is not recommended.

Plasma concentrations of didanosine may be reduced by methadone and increased by ganciclovir or valganciclovir, although the degree may vary with specific didanosine preparations. The paediatric powder for oral solution (*Videx; BMS, USA*) should not be given with methadone or ganciclovir, although the enteric-coated tablet (*Videx; BMS, USA*) could be used, if necessary, with careful monitoring.

Didanosine formulations (chewable or dispersible preparation) contain an antacid and other drugs that could be affected by an increased gastric pH (for example some HIV-protease inhibitors, ketoconazole, itraconazole, and fluoroquinolone antibacterials) should be given at least 2 hours before didanosine. Didanosine preparations containing magnesium or aluminium antacids should not be given with tetracyclines.

Use of didanosine with tenofovir results in increased plasma concentrations of didanosine and consequently an increased risk of didanosine-related adverse effects such as peripheral neuropathy, pancreatitis, and lactic acidosis. Fatalities have been reported. There have also been reports of virological failure and emergence of resistance at an early stage of treatment when didanosine and tenofovir were given with lamivudine as part of a once daily triple nucleoside regimen. UK licensed product information for both didanosine and tenofovir does not recommend co-administration of these drugs either at standard or reduced doses of didanosine. A 250-mg daily dose of didanosine had been evaluated, but resulted in virological failure and the emergence of resistance. US product information for didanosine, however, recommends that co-administration may be undertaken with caution in patients with normal renal function. For patients weighing greater than 60 kg the dose of didanosine should be reduced to 250 mg daily, while for those weighing less than 60 kg a dose of 200 mg daily is recommended. US product information for tenofovir advises against using didanosine with tenofovir in patients under 60 kg due to a lack of data.

Ribavirin has been shown *in vitro* to increase the intracellular triphosphate levels of didanosine and to potentially increase the risk of adverse effects related to didanosine; concurrent use should be avoided.

See also below for interactions with other antivirals.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; 37: 315–16.

Antivirals. Plasma concentrations of didanosine are roughly doubled when given with *ganciclovir*.[1-3] *Valganciclovir*, the prodrug of ganciclovir, inhibits purine nucleoside phosphorylase and increases didanosine concentrations. Significant CD4+ T lymphocyte count decline and symptoms of didanosine toxicity, despite complete viral suppression, occurred in an HIV-positive patient given an antiretroviral regimen containing didanosine plus valganciclovir for the treatment of CMV enteritis. Complete CD4 + count recovery and resolution of symptoms occurred when didanosine was replaced with abacavir.[4]

Changes in the pharmacokinetics of didanosine and *zidovudine* have occurred when these drugs are given together, but results of studies have not been consistent, and the effects have generally been of limited clinical significance. For further details, see under Interactions in Zidovudine, p. 1026.3.

Tenofovir has been reported to significantly increase plasma concentrations of didanosine,[5] (see also p. 973.3) and may increase the risk of pancreatitis associated with didanosine.[6,7] There has also been a report of acute renal failure and fatal lactic acidosis when tenofovir was added to a regimen containing didanosine.[8]

Use of didanosine with *delavirdine* resulted in reductions in the area under the concentration-time curve for both drugs in a single-dose study.[9] Licensed product information for delavirdine recommends that these two drugs should be given at least 1 hour apart.

Absorption of some *HIV-protease inhibitors* may be reduced by the buffers in some didanosine formulations and they should therefore be given 1 or more hours apart, depending on the drug (see p. 988.1).

1. Griffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; 10 (suppl 4): S3–S6.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; 38: 1057–62.
3. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 17: 227–34.
4. Tseng AL, Salit IE. CD4+ cell count decline despite HIV suppression: a probable didanosine-valganciclovir interaction. *Ann Pharmacother* 2007; 41: 512–17.
5. Pecora Fulco P, Kirlan MA. Effect of tenofovir on didanosine absorption in patients with HIV. *Ann Pharmacother* 2003; 37: 1325–8.
6. Blanchard JN, *et al.* Pancreatitis with didanosine and tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; 37: e57–e62. Correction. *Ibid.*: 995. [title of paper corrected]
7. Kirlan MA, *et al.* Acute onset of pancreatitis with concomitant use of tenofovir and didanosine. *Ann Pharmacother* 2004; 38: 1660–3.
8. Murphy MD, *et al.* Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis* 2003; 36: 1082–5.
9. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; 41: 169–74.

Antiviral Action

Didanosine is converted intracellularly to its active form dideoxyadenosine triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

Didanosine-resistant strains of HIV emerge during didanosine therapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. Evidence for the development of didanosine-resistant HIV was reported in 36 of 64 patients with advanced HIV infection within 24 weeks of switching from zidovudine to didanosine monotherapy.[1] Patients with the didanosine resistance mutation for HIV reverse transcriptase showed a greater decline in CD4+ T cell count and increase in viral burden than those without.

Multiple-drug resistant mutations have been found in patients taking long-term combination antiretroviral therapy containing didanosine.[2]

1. Kozal MJ, *et al.* Didanosine resistance in HIV-infected patients switched from zidovudine to didanosine monotherapy. *Ann Intern Med* 1994; 121: 263–8.
2. Kavlick MF, *et al.* Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; 98: 1506–13.

Pharmacokinetics

Didanosine is rapidly hydrolysed in the acid medium of the stomach and is therefore given orally with pH buffers or antacids. Bioavailability is reported to range from 20 to 40% depending on the formulation used; the bioavailability is substantially reduced with some formulations if taken with or after food. Peak plasma concentrations occur about 1 hour after oral dosage. Binding to plasma proteins is reported to be less than 5%. Didanosine has been reported not to cross the blood brain barrier.

Didanosine is metabolised intracellularly to the active antiviral metabolite dideoxyadenosine triphosphate. The plasma elimination half-life is reported to be about 1.5 hours. Renal clearance is by glomerular filtration and active tubular secretion; about 20% of an oral dose is recovered in the urine. Didanosine is partially cleared by haemodialysis but not by peritoneal dialysis.

References.

1. Balis FM, *et al.* Clinical pharmacology of 2',3'-dideoxyinosine in human immunodeficiency virus-infected children. *J Infect Dis* 1992; 165: 99–104.
2. Morse GD, *et al.* Comparative pharmacokinetics of antiviral nucleoside analogues. *Clin Pharmacokinet* 1993; 24: 101–23.
3. Mueller BU, *et al.* Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics* 1994; 94: 724–31.
4. Knupp CA, *et al.* Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: influence of hemodialysis and continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther* 1996; 60: 535–42.
5. Wintergerst U, *et al.* Lack of absorption of didanosine after rectal administration in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; 43: 699–701.
6. Abreu T, *et al.* Bioavailability of once- and twice-daily regimens of didanosine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2000; 44: 1375–6.
7. Hernández-Novoa B, *et al.* Effect of food on the antiviral activity of didanosine enteric-coated capsules: a pilot comparative study. *HIV Med* 2008; 9: 187–91.

Pregnancy. Fetal blood concentrations of 14 and 19% of the maternal serum-didanosine concentrations have been reported.[1] There is evidence of extensive metabolism in the placenta.[2]

1. Pons JC, *et al.* Fetoplacental passage of 2',3'-dideoxyinosine. *Lancet* 1991; 337: 732.
2. Dancis J, *et al.* Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J Acquir Immune Defic Syndr* 1993; 6: 2–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dinosin; Videx; *Austral.*: Videx; *Austria*: Videx; *Belg.*: Videx; *Braz.*: Videx; *Canad.*: Videx; *Chile*: Videx; *China*: Ai Lue (艾略); Hate (哈特); Videx (惠妥滋); ZhengYuan (正元); *Cz.*: Videx; *Denm.*: Videx; *Fin.*: Videx; *Fr.*: Videx; *Ger.*: Videx; *Gr.*: Videx; *Hong Kong*: Videx; *Hung.*: Videx; *India*: D-Sine; DDRetro; Dinex; *Indon.*: Videx†; *Irl.*: Videx; *Ital.*: Videx; *Malaysia*: Videx; *Mex.*: Didasten†; Dinocin; Videx; *Neth.*: Videx; *Norw.*: Videx; *NZ*: Videx; *Pol.*: Videx†; *Port.*: Videx; *Rus.*: Videx (Видекс); *S.Afr.*: Deladex; Videx; *Spain*: Videx; *Swed.*: Videx; *Switz.*: Videx; *Thai.*: Divir; Videx; *Turk.*: Videx; *UK*: Videx; *USA*: Videx; *Venez.*: Videx.

Multi-ingredient Preparations. *India*: Odivir Kit.

Pharmacopoeial Preparations

USP 36: Didanosine Delayed-Release Capsules; Didanosine for Oral Solution; Didanosine Tablets for Oral Suspension.

Docosanol *(USAN)*

Behenyl Alcohol; *n*-Docosanol; Docosyl Alcohol; IK-2; Докозанол.

1-Docosanol.

$C_{22}H_{46}O$=326.6

CAS — 661-19-8.

ATC — D06BB11.

ATC Vet — QD06BB11.

UNII — 9G1OE216XY.

Profile

Docosanol is an antiviral used topically five times daily as a 10% cream in the treatment of recurrent herpes labialis (see Herpes Simplex Infections, p. 955.2). Docosanol is reported to act by inhibiting fusion between the cell plasma membrane and the herpes simplex virus, thereby preventing viral entry into cells and subsequent viral replication. It has been investigated for genital herpes.

References.

1. Habbema L, *et al.* n-Docosanol 10% cream in the treatment of recurrent herpes labialis: a randomised, double-blind, placebo-controlled study. *Acta Derm Venereol* 1996; 76: 479–81.
2. Sacks SL, *et al.* Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2001; 45: 222–30.
3. Leung DT, Sacks SL. Docosanol: a topical antiviral for herpes labialis. *Expert Opin Pharmacother* 2004; 5: 2367–71.
4. Treister NS, Woo SB. Topical n-docosanol for management of recurrent herpes labialis. *Expert Opin Pharmacother* 2010; 11: 853–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Abreva; *Cz.*: Erazaban; *Fr.*: Erazaban; *Gr.*: Healip; *Irl.*: Erazaban; *Neth.*: Erazaban; *Norw.*: Heloc†; *Pol.*: Erazaban; *Port.*: Erazaban; *Swed.*: Healip†; *UK*: Blistex Cold Sore Cream; *Ukr.*: Priora (Приора); *USA*: Abreva.

Dolutegravir *(USAN, rINN)*

Dolutégravir; Dolutegravirum; GSK-1349572; S-349572; Долутеравир.

(4*R*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1′,2′:4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide.

$C_{20}H_{19}F_2N_3O_5$=419.4

CAS — 1051375-16-6.

UNII — DKO1W9H7M1.

Dolutegravir Sodium *(USAN, rINNM)*

Dolutegravir Sódico; Dolutégravir Sodique; GSK-1349572A; Natrii Dolutegravirum; Натрий Долутеравир.

$C_{20}H_{18}F_2N_3NaO_5$=441.4

CAS — 1051375-19-9.

UNII — 1Q1V9V5WYQ.

Profile

Dolutegravir is an inhibitor of HIV integrase, an enzyme essential for insertion of viral DNA into the host genome, and thus for replication. It is used with other antiretrovirals for treatment of HIV infection and AIDS (p. 957.2) and is licensed for use in both treatment-naive and treatment-experienced patients.

It is given orally as the sodium salt but doses are expressed in terms of the free acid; 52.6 mg of dolutegravir sodium is equivalent to about 50 mg of dolutegravir. The usual dose is the equivalent of 50 mg of dolutegravir once daily, given with or without food. When used in integrase strand transfer inhibitor (INSTI)-experienced patients with certain INSTI-associated resistance substitutions or suspected INSTI resistance, a dose of 50 mg twice daily is recommended. This dose is also suggested when dolutegravir is given with efavirenz, ritonavir-boosted fosamprenavir or tipranavir, or rifampicin.

Dolutegravir increases the serum concentration of dofetilide (p. 1367.1) with the possible risk of serious and/or life-threatening events.

References.

1. Ballantyne AD, Perry CM. Dolutegravir: first global approval. *Drugs* 2013; 73: 1627–37.

2. Cahn P, *et al.* Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet* 2013; **382:** 700–8.
3. Raffi F, *et al.* Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013; **13:** 927–35.
4. Eron JJ, *et al.* Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *J Infect Dis* 2013; **207:** 740–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Tivicay.

Efavirenz *(BAN, rINN)*

SB706; DMP-266; Efavirentsi; Éfavirenz; Efavirenzum; Efawirenz; L-743; L-743726; Эфавиренз.

(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

$C_{14}H_9ClF_3NO_2$=315.7

CAS — *154598-52-4.*

ATC — *J05AG03.*

ATC Vet — *QJ05AG03.*

UNII — *JE6H2O27P8.*

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Efavirenz). A white to slightly pink crystalline powder. Practically insoluble in water; soluble in methyl alcohol. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Efavirenz is a non-nucleoside reverse transcriptase inhibitor with activity against HIV. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS (p. 957.2).

Efavirenz is given orally as *capsules* or *tablets* in a dose of 600 mg once daily; alternatively, it may be given as an *oral solution* in a dose of 720 mg once daily. Efavirenz tablets and capsules should be given on an empty stomach. Dosing at bedtime is recommended during the first 2 to 4 weeks of therapy to improve tolerability. Bioavailability of efavirenz from the oral solution is less than that from the capsule and so proportionately higher doses of the solution are used.

Licensed product information notes that the dose of efavirenz may need to be adjusted to manage significant drug interactions:

- a decreased dose of 300 mg once daily is recommended when efavirenz is given with voriconazole (in contrast, the maintenance dose of voriconazole should be increased; for details, see Uses and Administration of Voriconazole, p. 597.2)
- for use with rifampicin, the dose of efavirenz should be increased to 800 mg daily in patients weighing 50 kg or more

For a dose-escalation protocol suggested to reduce efavirenz-related neuropsychiatric adverse effects, see Effects on the Nervous System, below.

For details of doses in children and adolescents, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing efavirenz in combination with emtricitabine and tenofovir are available in some countries.

References.
1. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. *Drugs* 2006; **66:** 1501–12.
2. Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. *J Antimicrob Chemother* 2009; **64:** 910–28.
3. Mbuagbaw LCE, *et al.* Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naive individuals. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 26/01/11).
4. Deeks ED, Perry CM. Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla): a review of its use in the management of HIV infection. *Drugs* 2010; **70:** 2315–38.

Administration. The bioavailability of a single 600-mg dose of efavirenz given as the capsule contents sprinkled and mixed with a small amount of suitable food vehicle (such as apple sauce, grape jelly, yogurt, or infant formula) was found to be bioequivalent to a 600-mg efavirenz dose given as intact capsules under fasting conditions in healthy adults.[1]

1. Kaul S, *et al.* Bioavailability in healthy adults of efavirenz capsule contents mixed with a small amount of food. *Am J Health-Syst Pharm* 2010; **67:** 217–22.

Administration in children. For the treatment of HIV infection in children 3 years of age and older and adolescents efavirenz is given daily with other antiretroviral drugs. In the USA oral *capsules* and *tablets* are available and the dose is based on body-weight:

- 10 to 14 kg: 200 mg once daily
- 15 to 19 kg: 250 mg once daily
- 20 to 24 kg: 300 mg once daily
- 25 to 32.4 kg: 350 mg once daily
- 32.5 to 39 kg: 400 mg once daily
- 40 kg or more: as for adults (above)

Capsules are also available in the UK for use in children and adolescents; doses are similar to those used in the USA.

In the UK an *oral solution* is also available; the dose ranges, which are again calculated in terms of body-weight, also depend on the age range:

- 13 to 14 kg: children less than 5 years, 360 mg daily; children 5 years and older, 270 mg once daily
- 15 to 19 kg: children less than 5 years, 390 mg daily; children 5 years and older, 300 mg once daily
- 20 to 24 kg: children less than 5 years, 450 mg daily; children 5 years and older, 360 mg once daily
- 25 to 32.4 kg: children less than 5 years, 510 mg daily; children 5 years and older, 450 mg once daily
- 32.5 to 39 kg: children 5 years and older, 510 mg once daily
- 40 kg or more: children 5 years and older, as for adults, above

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing efavirenz are rashes and psychiatric or CNS disturbances. Mild to moderate rashes (usually maculopapular eruptions) generally appear within the first 2 weeks of starting therapy and may resolve within a month of continued treatment; severe forms including erythema multiforme and Stevens-Johnson syndrome have been reported occasionally. Adverse CNS include agitation, amnesia, confusion, dizziness, euphoria, headache, insomnia or somnolence, impaired concentration, abnormal thinking or dreaming, convulsions, depersonalisation, and hallucinations. Such effects usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks; they may occur more frequently when efavirenz is taken with meals, possibly due to increased efavirenz plasma concentrations. Serious psychiatric adverse effects include severe depression, suicidal ideation and attempts, aggressive behaviour, and psychotic reactions including paranoia and mania. Other adverse effects include nausea and vomiting, diarrhoea, fatigue, and pancreatitis. Raised liver enzyme values and raised serum-cholesterol and -triglyceride concentrations have been reported. Hepatic failure and photoallergic dermatitis have occurred.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including efavirenz, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including efavirenz. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported.

Effects on the mouth. Burning mouth syndrome was diagnosed in a patient 2 weeks after adding efavirenz to her long-standing combination antiretroviral treatment regimen.[1] Efavirenz was stopped and the syndrome resolved within 1 week.

1. Borrás-Blasco J, *et al.* Burning mouth syndrome due to efavirenz therapy. *Ann Pharmacother* 2006; **40:** 1471–2.

Effects on the nervous system. More than 50% of patients starting efavirenz therapy have efavirenz-related neuropsychiatric adverse events. These may be severe enough to lead to patients stopping treatment, although the risk of exacerbating anxiety or depression has been questioned. Symptoms are generally transient and resolve within 4 weeks of beginning therapy.[1] The results of a randomised, double-blind, multicentre study,[2] suggested that step-wise dose escalation of oral efavirenz over 2 weeks (200 mg daily on days 1 to 6, 400 mg daily on days 7 to 13, and 600 mg daily on day 14 and beyond) might reduce the incidence and intensity of efavirenz-related neuropsychiatric adverse effects, with no apparent decrease in antiviral efficacy. However, there has been some concern about longer term neurotoxicity. A cohort study[3] in 146 asymptomatic HIV-infected subjects, most of whom had been receiving combination antiretroviral therapy for more than a year, found that about half of them had some degree of cognitive impairment, and this was strongly associated with use of efavirenz.

1. Clifford DB, *et al.* Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005; **143:** 714–21.
2. Gutiérrez-Valencia A, *et al.* Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. *Ann Intern Med* 2009; **151:** 149–56.
3. Ciccarelli N, *et al.* Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011; **76:** 1403–9.

Effects on vitamin D metabolism. In a cross-sectional study of 1077 HIV-infected patients,[1] inclusion of efavirenz in antiretroviral regimens was found to nearly double the risk of severe vitamin D deficiency. A subsequent observational cohort study[2] also found an association between vitamin D insufficiency and use of an efavirenz-based antiretroviral regimen.

1. Welz T, *et al.* Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *AIDS* 2010; **24:** 1923–8.
2. Dao CN, *et al.* Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. *Clin Infect Dis* 2011; **52:** 396–405.

Hyperhidrosis. Severe night sweats in a patient being treated with efavirenz resolved when the dose was reduced; the patient had higher than normal plasma-efavirenz concentrations at standard dosage, perhaps due to a abnormal allele of the cytochrome P450 isoenzyme CYP2D6.[1]

1. Martín AF, *et al.* Hyperhidrosis in association with efavirenz. *AIDS Patient Care STDS* 2009; **23:** 143–5.

Hypersensitivity. Hypersensitivity syndromes suggestive of DRESS (drug rash with eosinophilia and systemic symptoms) have been reported with efavirenz;[1-5] systemic symptoms may include renal impairment, respiratory failure, and hepatitis. In some cases, systemic manifestations have occurred without evident rash or eosinophilia.[3]

1. Bossi P, *et al.* Hypersensitivity syndrome associated with efavirenz therapy. *Clin Infect Dis* 2000; **30:** 227–8.
2. Behrens GM, *et al.* Pulmonary hypersensitivity reaction induced by efavirenz. *Lancet* 2001; **357:** 1503–4. Correction. *ibid.*; 2060.
3. Angel-Moreno-Maroto A, *et al.* Severe efavirenz-induced hypersensitivity syndrome (not-DRESS) with acute renal failure. *J Infect* 2006; **52:** e39–e40.
4. Curry E, *et al.* Renal impairment and hypersensitivity reaction due to efavirenz. *Nephrology (Carlton)* 2008; **13:** 541.
5. Leung JM, *et al.* Efavirenz-induced hypersensitivity reaction manifesting in rash and hepatitis in a Latino male. *Ann Pharmacother* 2008; **42:** 425–9.

Precautions

Efavirenz is contra-indicated in patients with severe hepatic impairment (Child-Pugh class C), and is not recommended in those with moderate impairment; it should be used with caution, and liver enzymes values monitored, in patients with mild liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution should be exercised in patients with a history of seizures or psychiatric disorders including depression. Efavirenz should be stopped if a severe rash, associated with blistering, desquamation, mucosal involvement, or fever, develops. Monitoring of serum lipids and blood-glucose may be considered during efavirenz treatment. Food may increase exposure to efavirenz and lead to an increase in the frequency of undesirable effects.

False-positive results in some urinary cannabinoid tests have been reported in subjects receiving efavirenz.

Abuse. Efavirenz has reportedly been used as an ingredient in 'Whoonga', a highly addictive street drug used in some parts of Africa to enhance the hallucinogenic effects of cannabis (p. 2467.1). These reports have been questioned by some authorities, citing tests of samples from South Africa where no efavirenz was identified.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies efavirenz as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Licensed product information states that efavirenz has been associated with teratogenicity in *animals.* No specific malformation pattern was noted in more than 500 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen. However, retrospective analysis of these pregnancies noted a few cases of neural tube defects, including meningomyelocele. US guidelines for use of antiretroviral drugs in pregnant HIV-infected women[1] recommend that use of efavirenz be avoided in the first trimester, although use later in the

pregnancy may be considered if no better alternatives exist. The use of adequate contraceptive measures is recommended during, and for 12 weeks after, treatment with regimens containing efavirenz.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Efavirenz is metabolised mainly by cytochrome P450 isoenzymes including CYP3A4. Consequently, it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Enzyme inducers may decrease plasma concentrations of efavirenz; efavirenz itself acts as an enzyme inducer and can reduce plasma concentrations of other drugs. Inhibition of some P450 isoenzymes has also been found *in vitro*.

Efavirenz is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antihistamines (astemizole and terfenadine), calcium-channel blockers (bepridil), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (midazolam and triazolam). St John's wort decreases the concentration of efavirenz; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Antibacterials. Plasma concentrations of efavirenz may be reduced by *rifampicin* and may necessitate an increase in the dose of efavirenz; for specific dosing guidance, see Uses and Administration, p. 975.1. Concurrent use with *rifabutin* does not appear to significantly affect efavirenz concentrations, but for the effect of efavirenz on rifabutin, see p. 350.1.

Use of efavirenz with *clarithromycin* has resulted in a decrease in the plasma concentration of clarithromycin and an increase in its active hydroxy metabolite. The combination has been associated with a high incidence of rashes.

Antiepileptics. A small crossover study[1] in healthy subjects reported that both efavirenz and carbamazepine exposure was significantly reduced when efavirenz 600 mg daily was given with carbamazepine titrated to 400 mg daily. Both drugs are metabolised by cytochrome P450 isoenzymes and they appear to induce each other's metabolism. However, no significant effect was seen in the pharmacokinetics of the 10,11-epoxide metabolite of carbamazepine. It was recommended that an alternative antiepileptic drug (such as vigabatrin or gabapentin) be considered or the dose of carbamazepine be titrated to a higher dose if given with efavirenz.

1. Ji P, *et al.* Pharmacokinetic interaction between efavirenz and carbamazepine after multiple-dose administration in healthy subjects. *J Clin Pharmacol* 2008; **48**: 948–56.

Antifungals. When efavirenz and *voriconazole* are given together the concentration of efavirenz is increased and that of voriconazole reduced.[1] For the adjusted doses recommended for managing this interaction, see Uses and Administration of Efavirenz (p. 975.1) and Voriconazole (p. 597.2).

Efavirenz also significantly decreased the concentrations of *itraconazole* and *posaconazole*; as no suitable dose adjustments for these drugs have been established, use of alternative antifungals should be considered. Efavirenz may also have the potential to decrease concentrations of *ketoconazole*.

1. Damle B, *et al.* Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. *Br J Clin Pharmacol* 2008; **65**: 523–30.

Antivirals. For the effect of efavirenz on *HIV-protease inhibitors*, see p. 988.1.

Grapefruit. The metabolism of efavirenz may be inhibited by concomitant ingestion of grapefruit juice.

Antiviral Action

Efavirenz acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to efavirenz and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Efavirenz is absorbed after oral doses and peak plasma concentrations occur after about 3 to 5 hours. Steady-state plasma concentrations are reached in 6 to 7 days after multiple dosing. Food increases the bioavailability of efavirenz. Efavirenz is more than 99% bound to plasma proteins and is distributed into the CSF. It is metabolised mainly by hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2B6 into inactive hydroxylated, metabolites. Efavirenz acts as an enzyme inducer and induces its own metabolism resulting in a terminal half-life of 40 to 55 hours after multiple doses compared with 52 to 76 hours after a single dose. About 14 to 34% of a dose is excreted in the urine (less than 1% unchanged), and 16 to 61% in the faeces (mainly as unchanged drug).

References.
1. Kappelhoff BS, *et al.* Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2005; **44**: 849–61.
2. Almond LM, *et al.* Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. *J Antimicrob Chemother* 2005; **56**: 738–44.
3. Burger D, *et al.* Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* 2006; **61**: 148–54.
4. Back DJ, *et al.* Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2006; **45**: 213–14.
5. Wintergerst U, *et al.* Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother* 2008; **61**: 1336–9.
6. Ngaimisi E, *et al.* Long-term efavirenz autoinduction and its effect on plasma exposure in HIV patients. *Clin Pharmacol Ther* 2010; **88**: 676–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Efavilea†; Filginase; Stocrin; Sulfinav; Virorrever; Zuletel; ***Austral.***: Stocrin; ***Austria***: Stocrin; ***Belg.***: Stocrin; ***Braz.***: Evir; Stocrin; ***Canad.***: Sustiva; ***Chile***: Stocrin; ***China***: Stocrin (施多宁); *Cz.*: Stocrin; Sustiva; ***Denm.***: Stocrin; ***Fin.***: Stocrin; ***Fr.***: Sustiva; ***Ger.***: Sustiva; ***Gr.***: Stocrin; Sustiva; ***Hong Kong***: Stocrin; ***Hung.***: Stocrin; ***India***: EP; Efavir; Efcure; Efferven; Evirenz; ***Irl.***: Stocrin; Sustiva; ***Israel***: Stocrin; ***Ital.***: Sustiva; ***Malaysia***: Stocrin; ***Mex.***: Stocrin; ***Neth.***: Stocrin; Sustiva; ***Norw.***: Stocrin; ***NZ***: Stocrin; ***Pol.***: Stocrin; Sustiva; ***Port.***: Stocrin; Sustiva; ***Rus.***: Stocrin (Стокрин); ***S.Afr.***: Erige; Hevaz; Stocrin; ***Singapore***: Stocrin; ***Spain***: Sustiva; ***Swed.***: Stocrin; ***Switz.***: Stocrin; ***Thai.***: Stocrin; ***Turk.***: Stocrin; ***UK***: Sustiva; ***USA***: Sustiva; ***Venez.***: Efavir; Stocrin.

Multi-ingredient Preparations. ***Austral.***: Atripla; ***Austria***: Atripla; ***Belg.***: Atripla; ***Canad.***: Atripla; *Cz.*: Atripla; ***Denm.***: Atripla; ***Fr.***: Atripla; ***Ger.***: Atripla; ***Gr.***: Atripla; ***Hong Kong***: Atripla; ***India***: Cytocom-E; Duovir-E; Emduo-E; Lazid-E; Odivir Kit; ***Irl.***: Atripla; ***Israel***: Atripla; ***Ital.***: Atripla; ***Neth.***: Atripla; ***Norw.***: Atripla; ***NZ***: Atripla; ***Pol.***: Atripla; ***Port.***: Atripla; ***Spain***: Atripla; ***Swed.***: Atripla; ***Switz.***: Atripla; ***Thai.***: Atripla; ***UK***: Atripla; ***USA***: Atripla.

Pharmacopoeial Preparations
USP 36: Efavirenz Capsules.

Elvitegravir *(USAN, rINN)*

Elvitégravir; Elvitegravirum; GS-9137; JTK-303; Эльвитегравир.

6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

$C_{23}H_{23}ClFNO_5$=447.9

CAS — 697761-98-1.

ATC — J05AX11.

ATC Vet — QJ05AX11.

UNII — 4GDQ854U53.

Profile

Elvitegravir is an HIV-integrase inhibitor with antiretroviral activity against HIV-1. Elvitegravir (150 mg) may be given as a component of a four-drug, fixed-dose combination product (*Stribild, Gilead, USA* and also referred to as the Quad pill) with the pharmacokinetic enhancer cobicistat (p. 2482.3) and the NRTIs emtricitabine (below) and tenofovir (p. 1018.1) for the treatment of HIV infection and AIDS (p. 957.2) in antiretroviral treatment-naive patients. The recommended dose is one tablet taken orally once daily with food. It is also being studied with low-dose ritonavir acting as a pharmacokinetic enhancer.

Elvitegravir is metabolised by the cytochrome P450 isoenzyme CYP3A and drugs that induce CYP3A may decrease its plasma concentration, while drugs that inhibit CYP3A may increase its plasma concentration. It is also a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

References.
1. Ramanathan S, *et al.* Pharmacokinetics of coadministered ritonavir-boosted elvitegravir and zidovudine, didanosine, stavudine, or abacavir. *J Acquir Immune Defic Syndr* 2007; **46**: 160–6.
2. Shimura K, *et al.* Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *J Virol* 2008; **82**: 764–74.
3. Shimura K, Kodama EN. Elvitegravir: a new HIV integrase inhibitor. *Antiviral Chem Chemother* 2009; **20**: 79–85.
4. Klibanov OM. Elvitegravir, an oral HIV integrase inhibitor, for the potential treatment of HIV infection. *Curr Opin Investig Drugs* 2009; **10**: 190–200.
5. Zolopa AR, *et al.* Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. *J Infect Dis* 2010; **201**: 814–22.
6. Ramanathan S, *et al.* Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet* 2011; **50**: 229–44.
7. Olin JL, *et al.* Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet for HIV-1 infection treatment. *Ann Pharmacother* 2012; **46**: 1671–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Vitekta.

Multi-ingredient Preparations. *Jpn*: Stribild; *UK*: Stribild; *USA*: Stribild.

Emtricitabine *(USAN, rINN)*

BW-524W91; Emtricitabin; Emtricitabina; Emtricitabinum; Emtrisitabin; (-)-FTC; FTC-(-); FTC; Эмтрицитабин.

5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

$C_8H_{10}FN_3O_3S$=247.2

CAS — 143491-57-0.

ATC — J05AF09.

ATC Vet — QJ05AF09.

UNII — G70B4ETF4S.

Uses and Administration

Emtricitabine is a nucleoside reverse transcriptase inhibitor related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when emtricitabine is used alone, and it is therefore used with other antiretrovirals.

Emtricitabine is given orally once daily as capsules in a usual adult dose of 200 mg or 240 mg as oral solution.

For details of doses in infants, children, and adolescents, see below.

For details of doses of emtricitabine to be used in patients with renal impairment, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing emtricitabine with tenofovir, and with efavirenz plus tenofovir are available in some countries. It is also a component of a four-drug, fixed-dose combination product with elvitegravir and tenofovir and the pharmacokinetic enhancer cobicistat (p. 2482.3).

Reviews.
1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64**: 2075–82.
2. Modrzejewski KA, Herman RA. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. *Ann Pharmacother* 2004; **38**: 1006–14.
3. Prampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. *Drugs* 2005; **65**: 1427–48.
4. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. *Clin Infect Dis* 2006; **42**: 126–31.
5. Perry CM. Emtricitabine/tenofovir disoproxil fumarate: in combination with a protease inhibitor in HIV-1 infection. *Drugs* 2009; **69**: 843–57.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents emtricitabine is given with other antiretroviral drugs. Doses, given once daily, are based on body-weight:

- in infants up to 3 months of age the *oral solution* is given in a dose of 3 mg/kg daily
- in infants, children, and adolescents over 3 months of age the oral solution is given in a dose of 6 mg/kg daily to a maximum daily dose of 240 mg
- the *capsules* may be given to children and adolescents weighing more then 33 kg in the usual adult dose of 200 mg daily.

Administration in renal impairment. Doses of emtricitabine should be reduced in patients with renal impairment, according to the patient's creatinine clearance (CC):

- CC at least 50 mL/minute: usual adult doses (as capsules or solution)
- CC 30 to 49 mL/minute: 200 mg every 48 hours (capsules) or 120 mg every 24 hours (oral solution)
- CC 15 to 29 mL/minute: 200 mg every 72 hours (capsules) or 80 mg every 24 hours (oral solution)
- CC less than 15 mL/minute: 200 mg every 96 hours (capsules) or 60 mg every 24 hours (oral solution)

Hepatitis B. For mention of the use of emtricitabine with tenofovir in the management of treatment-experienced patients with hepatitis B, see under Tenofovir, p. 1018.2.

Prevention of HIV transmission. For discussion of the use of emtricitabine with tenofovir to reduce transmission of HIV infection, see under Tenofovir, p. 1018.2.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing emtricitabine are headache, diarrhoea, and nausea; hyperpigmented skin discoloration is very common in children and common in adults. Other common adverse effects include abdominal pain, vomiting, dyspepsia, abnormal dreams, asthenia, dizziness, insomnia, pain, allergic skin reactions, pruritus, rashes, and urticaria. Abnormal laboratory test results associated with emtricitabine-containing regimens include hyperbilirubinaemia, increases in serum lipase and pancreatic amylase, and raised liver enzymes. There have also been reports of neutropenia and anaemia. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including emtricitabine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including emtricitabine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Precautions

Treatment with emtricitabine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Emtricitabine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events; treatment should be interrupted or stopped if there is evidence of exacerbation of liver disease. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment is begun. Acute and sometimes severe exacerbations of hepatitis have been reported in hepatitis B-infected patients after stopping treatment with emtricitabine; patients co-infected with HIV and hepatitis B should be closely monitored for several months after stopping treatment. Emtricitabine should be used with caution and doses adjusted in patients with renal impairment.

Interactions

Caution should be exercised when emtricitabine is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Emtricitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase. Emtricitabine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Emtricitabine is rapidly and extensively absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur after 1 to 2 hours. Bioavailability is reported to be 93% for the capsules. Binding to plasma proteins is reported to be less than 4%. The plasma elimination half-life is about 10 hours. Emtricitabine is metabolised to a limited degree, but is excreted largely unchanged in the urine and to a lesser extent in the faeces. It is partially removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Emtriva; ***Austral.***: Emtriva; ***Austria***: Emtriva; ***Belg.***: Emtriva; ***Canad.***: Emtriva; ***China***: Hui Er Ding (惠尔丁); Xin Luo Shu (新罗舒); *Cz.*: Emtriva; ***Denm.***: Emtriva; Eviplera; ***Fin.***: Emtriva; ***Fr.***: Emtriva; ***Ger.***: Emtriva; ***Gr.***: Emtriva; ***Hung.***: Emtriva; ***Irl.***: Emtriva; ***Ital.***: Emtriva; ***Mex.***: Emtriva; ***Neth.***: Emtriva; ***Norw.***: Emtriva; ***NZ***: Emtriva; ***Pol.***: Emtriva; ***Port.***: Emtriva; ***Spain***: Emtriva; ***Swed.***: Emtriva; ***Switz.***: Emtriva; ***UK***: Emtriva; ***USA***: Emtriva.

Multi-ingredient Preparations. *Arg.*: Truvada; ***Austral.***: Atripla; Truvada; ***Austria***: Atripla; Truvada; ***Belg.***: Atripla; Truvada; ***Canad.***: Atripla; Truvada; ***Chile***: Truvada; *Cz.*: Atripla; Truvada; ***Denm.***: Atripla; Truvada; ***Fin.***: Truvada; ***Fr.***: Atripla; Truvada; ***Ger.***: Atripla; Eviplera; Truvada; ***Gr.***: Atripla; Truvada; ***Hong Kong***: Atripla; Truvada; ***Irl.***: Atripla; Truvada; ***Israel***: Atripla; Eviplera; Truvada; ***Ital.***: Atripla; Truvada; ***Jpn***: Stribild; ***Mex.***: Truvada; ***Neth.***: Atripla; Truvada; ***Norw.***: Atripla; Eviplera; Truvada; ***NZ***: Atripla; Truvada; ***Pol.***: Atripla; Truvada; ***Port.***: Atripla; Truvada; ***S.Afr.***: Adco Emtevir; Didivir; Truvada; Tyricten; ***Spain***: Atripla; Truvada; ***Swed.***: Atripla; Eviplera; Truvada; ***Switz.***: Atripla; Eviplera; Truvada; ***Thai.***: Atripla; Ricovir-Em; Truvada; ***UK***: Atripla; Eviplera; Stribild; Truvada; ***USA***: Atripla; Complera; Stribild; Truvada.

Enfuvirtide *(BAN, USAN, rINN)*

DP-178; Enfuvirtid; Enfuvirtida; Enfuvirtidum; Enfuwirtyd; Pentafusida; Pentafuside; T-20; Энфувиртид.

$C_{204}H_{301}N_{51}O_{64}$=4491.9

CAS — 159519-65-0.

ATC — J05AX07.

ATC Vet — QJ05AX07.

UNII — 19OWO1T3ZE.

Uses and Administration

Enfuvirtide is a synthetic 36-amino acid peptide that blocks HIV cell fusion and viral entry. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS (p. 957.2). Enfuvirtide is given by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a usual dose of 90 mg twice daily. Each injection should be given at a different site from the preceding one. For details of doses in children and adolescents, see below.

References.

1. Oldfield V, *et al.* Enfuvirtide: a review of its use in the management of HIV infection. *Drugs* 2005; 65: 1139–60.
2. Reynes J, *et al.* TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS* 2007; 21: 533–43.
3. Wiznia A, *et al.* T20-310 Study Group. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J* 2007; 26: 799–805.
4. Rockstroh J, *et al.* Adherence to enfuvirtide and its impact on treatment efficacy. *AIDS Res Hum Retroviruses* 2008; 24: 141–8.
5. Saberi P, *et al.* Immunologic benefits of enfuvirtide in patients enrolled in a drug assistance program. *Ann Pharmacother* 2008; 42: 621–6.
6. Kitchen CM, *et al.* Enfuvirtide antiretroviral therapy in HIV-1 infection. *Ther Clin Risk Manag* 2008; 4: 433–9.
7. Makinson A, Reynes J. The fusion inhibitor enfuvirtide in recent antiretroviral strategies. *Curr Opin HIV AIDS* 2009; 4: 150–8.
8. Joly V, *et al.* Enfuvirtide: from basic investigations to current clinical use. *Expert Opin Pharmacother* 2010; 11: 2701–13.

Administration in children. For the treatment of HIV infection, enfuvirtide may be given to children 6 to 16 years of age by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a dose of 2 mg/kg twice daily (to a maximum of 90 mg twice daily). Each injection should be given at a different site from the preceding one.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing enfuvirtide are local injection site reactions with resultant pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis. These reactions have been reported to occur in 98% of patients, but only a small minority needed to stop therapy. Other very common adverse effects include nausea, diarrhoea, weight loss, and peripheral neuropathy. Anorexia, abdominal pain, constipation, pancreatitis, myalgia, weakness or loss of strength, lymphadenopathy, insomnia, depression, 'flu-like' illness, sinusitis, and conjunctivitis are also common. An increased incidence of some bacterial infections, in particular of pneumonia, has occurred in patients receiving enfuvirtide. Hypersensitivity reactions have occurred in about 1% of patients. Other adverse effects have included anxiety, hyperglycaemia, hypertriglyceridaemia, and eosinophilia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy in HIV-infected patients with severe immune deficiency. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

References.

1. Maggi P, *et al.* Cutaneous injection site reactions to long-term therapy with enfuvirtide. *J Antimicrob Chemother* 2004; 53: 678–81.
2. Morilla ME, *et al.* Localized amyloidosis at the site of enfuvirtide injection. *Ann Intern Med* 2009; 151: 515–16.
3. Kousignian I, *et al.* Does enfuvirtide increase the risk of bacterial pneumonia in patients receiving combination antiretroviral therapy? *J Antimicrob Chemother* 2010; 65: 138–44.
4. Wallace BJ, *et al.* Enfuvirtide injection site reactions: a clinical and histopathological appraisal. *Australas J Dermatol* 2011; 52: 19–26.

Precautions

Enfuvirtide should be stopped immediately and should not be restarted in patients who develop signs of a systemic hypersensitivity reaction. An increased incidence of some bacterial infections, in particular of pneumonia, has been seen and patients receiving enfuvirtide should be closely monitored for signs of pneumonia. UK licensed product information recommends that enfuvirtide be used with caution in patients with hepatic impairment and in those with moderate to severe renal impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Antiviral Action

Enfuvirtide is an HIV fusion inhibitor that interferes with entry of HIV into cells by binding to the gp41 subunit of the viral envelope glycoprotein, thereby inhibiting fusion of viral and cellular membranes. Strains of HIV with reduced susceptibility to enfuvirtide have been isolated in patients receiving the drug but, owing to the different mode of action of enfuvirtide and the fact that it does not require intracellular activation for its activity, cross-resistance with other antiretrovirals may occur less frequently.

Resistance. References to the development of resistance to enfuvirtide.

1. Greenberg ML, Cammack N. Resistance to enfuvirtide, the first HIV fusion inhibitor. *J Antimicrob Chemother* 2004; 54: 333–40.
2. van Lelyveld SF, *et al.* Therapy failure following selection of enfuvirtide-resistant HIV-1 in cerebrospinal fluid. *Clin Infect Dis* 2010; 50: 387–90.
3. Leung PH, *et al.* High prevalence of primary enfuvirtide (ENF) resistance-associated mutations in HIV-1-infected patients in Hong Kong. *J Clin Virol* 2010; 47: 273–5.

Pharmacokinetics

Enfuvirtide is absorbed after subcutaneous injection with a mean absolute bioavailability of 84%. It is 92% bound to plasma proteins. Enfuvirtide is a peptide and is metabolised by hydrolysis; it does not inhibit cytochrome P450 isoenzymes. The elimination half-life is 3.8 hours after subcutaneous use, although elimination pathways have yet to be identified.

References.

1. Patel IH, *et al.* Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clin Pharmacokinet* 2005; 44: 175–86.
2. Zhang X, *et al.* Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol* 2007; 47: 510–17.
3. Weizsaecker K, *et al.* Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS* 2011; 22: 294–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fuzeon; ***Austral.***: Fuzeon; ***Austria***: Fuzeon; ***Belg.***: Fuzeon; ***Braz.***: Fuzeon; ***Canad.***: Fuzeon; ***Chile***: Fuzeon; ***China***: Fuzeon (恩夫韦肽); *Cz.*: Fuzeon; ***Denm.***: Fuzeon; ***Fin.***: Fuzeon; ***Fr.***: Fuzeon; ***Ger.***: Fuzeon; ***Gr.***: Fuzeon; ***Hung.***: Fuzeon; ***Irl.***: Fuzeon; ***Israel***: Fuzeon; ***Ital.***: Fuzeon; ***Mex.***: Fuzeon; ***Neth.***: Fuzeon; ***Norw.***: Fuzeon†; ***NZ***: Fuzeon; ***Pol.***: Fuzeon; ***Port.***: Fuzeon; ***Rus.***: Fuzeon (Фузеон); ***Singapore***: Fuzeon; ***Spain***: Fuzeon; ***Swed.***: Fuzeon; ***Switz.***: Fuzeon; ***Thai.***: Fuzeon; ***UK***: Fuzeon; ***USA***: Fuzeon.

Entecavir *(USAN, rINN)*

BMS-200475-01; Entécavir; Entecavirum; SQ-34676; Энтекавир.

9-[(1*S*,3*R*,4*S*)-4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine monohydrate.

$C_{12}H_{15}N_5O_3.H_2O$=295.3

CAS — 142217-69-4 (anhydrous entecavir); 209216-23-9 (entecavir monohydrate).

ATC — J05AF10.

ATC Vet — QJ05AF10.

UNII — 5968Y6H45M (entecavir); NNU2O4609D (anhydrous entecavir).

Uses and Administration

Entecavir is a nucleoside reverse transcriptase inhibitor, structurally related to guanosine with selective antiviral activity against hepatitis B virus. It is used for the treatment of chronic hepatitis B (p. 952.1) in adults with compensated liver disease with evidence of active viral replication, persistently elevated liver enzyme values, and histologically active disease, including those resistant to lamivudine; it may also be used in those with decompensated liver disease. The usual oral dose of entecavir in patients with:

- compensated liver disease and who are nucleoside treatment-naive is 500 micrograms once daily, either with or without food. In patients with a history of hepatitis B viraemia during lamivudine therapy or with known resistance to lamivudine, a dose of 1 mg once daily on an empty stomach should be used
- decompensated liver disease is 1 mg once daily on an empty stomach

For details of reduced doses to be used in patients with renal impairment, see below.

Reviews.

1. Sims KA, Woodland AM. Entecavir: a new nucleoside analog for the treatment of chronic hepatitis B infection. *Pharmacotherapy* 2006; 26: 1745–57.
2. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; 28: 184–203.
3. Scott LJ, Keating GM. Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2009; 69: 1003–33.
4. Cornberg M, Manns MP. Entecavir—Möglichkeiten und Grenzen einer effektiven Therapie der chronischen Hepatitis B. *Dtsch Med Wochenschr* 2010; 135: 32–7.
5. Woo G, *et al.* Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010; 139: 1218–29.
6. Keating GM. Entecavir: a review of its use in the treatment of chronic hepatitis B in patients with decompensated liver disease. *Drugs* 2011; 71: 2511–29.

Administration in renal impairment. Oral doses of entecavir should be reduced in patients with renal impairment according to creatinine clearance (CC).

In those with compensated liver disease and a CC of:

- 30 to 49 mL/minute: 250 micrograms once daily or 500 micrograms every 48 hours in nucleoside treatment-naive patients; 500 micrograms once daily or 1 mg every 48 hours in lamivudine-refractory patients
- 10 to 29 mL/minute: 150 micrograms once daily or 500 micrograms every 72 hours in nucleoside treatment-naive patients; 300 micrograms once daily, 500 micrograms every 48 hours, or 1 mg every 72 hours in lamivudine-refractory patients
- less than 10 mL/minute (and patients on haemodialysis or continuous ambulatory peritoneal dialysis): 50 micrograms once daily or 500 micrograms every 5 to 7 days in nucleoside treatment-naive patients; 100 micrograms once daily, 500 micrograms every 72 hours, or 1 mg every 7 days in lamivudine-refractory patients

In those with decompensated disease, doses are the same as those for patients with lamivudine-resistant compensated disease.

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Adverse Effects

The most common adverse effects of entecavir have been headache, fatigue, dizziness, and nausea. Other adverse effects include diarrhoea, dyspepsia, insomnia, somnolence, and vomiting.

Raised liver enzyme concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with entecavir. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p. 1024.3). Patients with decompensated liver disease may be at a higher risk of serious hepatic adverse effects, lactic acidosis, and specific renal adverse effects such as hepatorenal syndrome.

Entecavir is carcinogenic in *rodents*, but a relationship with human cancer has not been established.

Precautions

Entecavir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Entecavir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients whose liver enzyme values increase due to response to treatment must be distinguished from those in whom this indicates toxicity. Exacerbation of hepatitis B has been reported both during and after stopping treatment with entecavir. Hepatic function should be monitored closely while on treatment and for several months after treatment is stopped. Dosage reduction may be necessary in patients with renal impairment.

Limited clinical experience suggests there is a potential for HIV to develop resistance to NRTIs if entecavir is used to treat chronic hepatitis B virus infection in patients with undiagnosed or untreated HIV infection. Treatment with entecavir is not recommended for co-infected patients who are not also receiving HAART. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with entecavir.

HIV-infected patients. It was initially thought that entecavir did not inhibit replication of HIV-1 at clinically relevant doses. However, a small consistent decrease in HIV-1 RNA was noted in 3 patients with HIV-1 and hepatitis B virus co-infection being treated with entecavir monotherapy.[1] In one of them, an HIV variant containing the M184V resistance substitution was found. Subsequent *in vitro* analyses showed that HIV-1 strains containing M184V were resistant to entecavir.

1. McMahon MA, *et al.* The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med* 2007; 356: 2614–21.

Interactions

Caution should be exercised when entecavir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Entecavir is phosphorylated intracellularly to the active triphosphate form which competes with deoxyguanosine triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby inhibiting every stage of the enzyme's activity.

Although initially thought to be inactive against HIV at clinically relevant doses, entecavir may have sufficient action to result in the selection of resistant HIV variants (see HIV-infected Patients, under Precautions, above).

Pharmacokinetics

Entecavir is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur 30 to 90 minutes after an oral dose and steady state concentrations after 6 to 10 days of treatment. Absorption is both delayed and reduced by food; this is not considered to be clinically relevant in nucleoside treatment-naive patients but may affect efficacy in lamivudine-refractory patients in whom entecavir should be taken on an empty stomach. Bioavailability of the tablet formulation is equal to that of the oral solution and they may be given interchangeably. Binding of entecavir to plasma proteins is about 13% *in vitro*. Entecavir is not metabolised by the cytochrome P450 system. It is mainly eliminated by the kidneys by glomerular filtration and active tubular secretion, with a terminal elimination half-life of 128 to 149 hours. Small amounts of glucuronide and sulfate conjugates are formed. Entecavir is partially removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Baraclude; Teneir; *Austral.*: Baraclude; *Austria*: Baraclude; *Belg.*: Baraclude; *Braz.*: Baraclude; *Canad.*: Baraclude; *Chile*: Baraclude; *China*: Baraclude (博路定); *Cz.*: Baraclude; *Denm.*: Baraclude; *Fr.*: Baraclude; *Ger.*: Baraclude; *Gr.*: Baraclude; *Hong Kong*: Baraclude; *Hung.*: Baraclude; *India*: Baraclude; *Indon.*: Baraclude; *Irl.*: Baraclude; *Israel*: Baraclude; *Ital.*: Baraclude; *Malaysia*: Baraclude; *Neth.*: Baraclude; *Norw.*: Baraclude; *NZ*: Baraclude; *Philipp.*: Baraclude; *Pol.*: Baraclude; *Port.*: Baraclude; *Rus.*: Baraclude (Бараклюд); *S.Afr.*: Baraclude; *Singapore*: Baraclude; *Spain*: Baraclude; *Swed.*: Baraclude; *Switz.*: Baraclude; *Thai.*: Baraclude; *Turk.*: Baraclude; *UK*: Baraclude; *USA*: Baraclude.

Etravirine *(BAN, USAN, rINN)*

Etravirin; Etravirina; Étravirine; Etravirinum; R-165335; TMC-125; Этравирин.

4-[6-Amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile.

$C_{20}H_{15}BrN_6O$=435.3

CAS — 269055-15-4.

ATC — J05AG04.

ATC Vet — QJ05AG04.

UNII — 0C50HW4FO1.

Uses and Administration

Etravirine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is given with other antiretrovirals for the treatment of HIV infection and AIDS (p. 957.2) in treatment-experienced patients, who have evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretrovirals. Etravirine is given orally in a usual dose of 200 mg twice daily after food.

For details of doses in children and adolescents, see below.

References.

1. Deeks ED, Keating GM. Etravirine. *Drugs* 2008; 68: 2357–72.
2. Johnson LB, Saravolatz LD. Etravirine, a next-generation nonnucleoside reverse-transcriptase inhibitor. *Clin Infect Dis* 2009; 48: 1123–8.
3. Harris M, *et al.* Canadian consensus guidelines for the optimal use of etravirine in the treatment of HIV-infected adults. *Can J Infect Dis Med Microbiol* 2009; 20: e24–e34.
4. Martínez E, Nelson M. Simplification of antiretroviral therapy with etravirine. *AIDS Rev* 2010; 12: 52–9.
5. Tseng A, Macarthur RD. Profile of etravirine for the treatment of HIV infection. *Ther Clin Risk Manag* 2010; 6: 49–58.
6. Towner W, *et al.* Efficacy, safety, and tolerability of etravirine with and without darunavir/ritonavir or raltegravir in treatment-experienced patients: analysis of the etravirine early access program in the United States. *J Acquir Immune Defic Syndr* 2010; 53: 614–18.
7. Elsayed RK, Caldwell DJ. Etravirine: a novel nonnucleoside reverse transcriptase inhibitor for managing human immunodeficiency virus infection. *Am J Health-Syst Pharm* 2010; 67: 193–205.

Licensed product information states etravirine tablets may be dispersed in a suitable liquid in patients with swallowing difficulties. The tablets should first be dispersed in a small amount of water (about 5 mL or just enough to cover tablet); thereafter, the mixture may be further diluted with more water, orange juice, or milk, although the use of grapefruit juice, and warm or carbonated beverages should be avoided. The mixture should be stirred well and the entire contents given to the patient immediately after preparation.

Administration in children. Etravirine is given orally with other antiretroviral drugs in the management of HIV infection and AIDS in treatment-experienced children and adolescents aged 6 to 18 years. Doses should be taken after food and are based on body-weight:

- 16 to less than 20 kg: 100 mg twice daily
- 20 to less than 25 kg: 125 mg twice daily
- 25 to less than 30 kg: 150 mg twice daily
- at least 30 kg: 200 mg twice daily (maximum dose)

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing etravirine are nausea and rash (usually mild to moderate) and generally appearing in the second week of treatment and resolving within 1 to 2 weeks. Severe and potentially life-threatening skin reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Severe systemic hypersensitivity reactions (DRESS syndrome—drug rash with eosinophilia and systemic symptoms), including cases resulting in liver failure, have also occurred. There have also been reports of rhabdomyolysis. Additional adverse events of moderate to severe intensity reported by at least 2% of patients receiving etravirine in clinical studies included gastrointestinal complaints (abdominal pain, diarrhoea, nausea, and vomiting), fatigue, headache, hypertension, and peripheral neuropathy. Raised liver enzyme values, glucose levels, and serum-cholesterol and -triglyceride concentrations have been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including etravirine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including etravirine.

General references.

1. Grinsztejn B, *et al.* A review of the safety and tolerability profile of the next-generation NNRTI etravirine. *AIDS Res Hum Retroviruses* 2010; 26: 725–33.

Precautions

Etravirine should be stopped immediately if a severe skin reaction or other signs or symptoms of hypersensitivity occur, including severe rash or rash accompanied by fever, malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, or eosinophilia. Etravirine is not recommended in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution in patients with mild to moderate liver disease. Patients who have virologic failure on a NNRTI-containing regimen should not be given etravirine in a regimen containing only NRTIs.

Interactions

Etravirine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19. It is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19. Consequently it may compete with other drugs metabolised by these systems, potentially resulting in

mutually altered plasma concentrations and possibly toxicity. Enzyme inducers may decrease plasma concentrations of etravirine. Carbamazepine, phenobarbital, phenytoin, rifampicin, rifapentine, and St John's wort may significantly decrease the concentration of etravirine; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Etravirine should not be given with other NNRTIs or with HIV-protease inhibitors given without ritonavir-boosting. US licensed product information also recommends that use with ritonavir-boosted atazanavir, fosamprenavir, or tipranavir be avoided; however, UK licensed product information suggests that ritonavir-boosted atazanavir may be used with etravirine and requires no dose adjustment, and that ritonavir-boosted fosamprenavir may also be used, although dose reductions may be required.

Reviews.
1. Kakuda TN, *et al.* Pharmacokinetic interactions between etravirine and non-antiretroviral drugs. *Clin Pharmacokinet* 2011; **50:** 25–39.

Antibacterials. For information on the interactions of etravirine with *rifabutin* and *rifampicin*, see p. 350.1 and p. 353.2 respectively.

Antiviral Action

Etravirine acts by inhibition of HIV-1 reverse transcriptase and blocks viral RNA- and DNA-dependent DNA polymerase activities. It is a flexible molecule designed to fit in the active pocket of viral reverse transcriptase in different ways, even when the shape of that pocket changes because of viral mutations. This is considered to reduce the risk of the development of resistance; phase II studies in treatment-experienced patients have shown activity against HIV resistant to other NNRTIs (delavirdine, efavirenz, and nevirapine).

Pharmacokinetics

Etravirine is readily absorbed after oral doses and peak plasma concentrations occur after about 2.5 to 4 hours; absorption is increased by food. It is about 99.9% bound to plasma proteins. Etravirine is extensively metabolised by hepatic microsomal enzymes, mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19 families, to substantially less active metabolites. The mean plasma half-life after usual dosage is about 41 hours and ranges from 21 to 61 hours. About 93.7% of a dose appears in the faeces (81.2 to 86.4% as unchanged drug), and 1.2% in the urine (unchanged drug was not detected in the urine).

References.
1. Schöller-Gyüre M, *et al.* Clinical pharmacokinetics and pharmacodynamics of etravirine. *Clin Pharmacokinet* 2009; **48:** 561–74.
2. Kakuda TN, *et al.* Pharmacokinetics and pharmacodynamics of the non-nucleoside reverse-transcriptase inhibitor etravirine in treatment-experienced HIV-1-infected patients. *Clin Pharmacol Ther* 2010; **88:** 695–703.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Intelence; ***Austral.***: Intelence; ***Austria***: Intelence; ***Belg.***: Intelence; ***Braz.***: Intelence; ***Canad.***: Intelence; ***Chile***: Intelence; ***China***: Intelence (英特莱); ***Cz.***: Intelence; ***Denm.***: Intelence; ***Fr.***: Intelence; ***Ger.***: Intelence; ***Gr.***: Intelence; ***Hung.***: Intelence; ***Irl.***: Intelence; ***Israel***: Intelence; ***Ital.***: Intelence; ***Neth.***: Intelence; ***Norw.***: Intelence; ***NZ***: Intelence; ***Pol.***: Intelence; ***Port.***: Intelence; ***Rus.***: Intelence (Интелленс); ***Spain***: Intelence; ***Swed.***: Intelence; ***Switz.***: Intelence; ***Thai.***: Intelence; ***UK***: Intelence; ***USA***: Intelence.

Famciclovir *(BAN, USAN, rINN)*

AV-42810; BRL-42810; Famciclovirum; Famciklor; Famsiklovir; Famsiklovir; Famciclovir; Фамцикловир.

2[2-(2-Amino-9*H*-purin-9-yl)ethyl]trimethylene diacetate.

$C_{14}H_{19}N_5O_4$=321.3

CAS — 104227-87-4.

ATC — J05AB09; S01AD07.

ATC Vet — QJ05AB09; QS01AD07.

UNII — QIC03ANI02.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Famciclovir). A white to pale yellow solid. Freely soluble in methyl alcohol and in acetone; sparingly soluble in alcohol and in isopropyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Famciclovir is a prodrug of the antiviral penciclovir (p. 1008.2). It is given orally in the treatment of herpes zoster (see Varicella-zoster Infections, p. 956.2) and genital and mucocutaneous herpes (see Herpes Simplex Infections, p. 955.2).

For **herpes zoster**, famciclovir is given in a dose of 500 mg three times daily for 7 days; immunocompromised patients are given 500 mg three times daily for 10 days.

For **herpes simplex infections**, famciclovir is given in a dose of 250 mg three times daily for 5 days for first episodes of genital herpes; immunocompromised patients may be given 500 mg twice daily for 7 days. For acute treatment of recurrent episodes of genital herpes, 125 mg is given twice daily for 5 days (in the USA, the recommended dose is 1 g twice daily for 1 day and the *BNF* also gives this as an alternative regimen). Treatment should start in the prodromal period as soon as the first signs or symptoms appear. Immunocompromised patients may be given 500 mg twice daily for 7 days. For suppression of recurrent episodes of genital herpes, 250 mg is given twice daily; immunocompromised patients may be given 500 mg twice daily. Such suppressive treatment is interrupted every 6 to 12 months to observe possible changes in the natural history of the disease.

For acute treatment of recurrent mucocutaneous herpes in HIV-infected patients, 500 mg is given twice daily for 7 days.

In the USA, famciclovir may also be given orally for the treatment of recurrent herpes labialis as a single 1.5 g dose, preferably begun in the prodromal period.

Doses of famciclovir should be reduced in patients with renal impairment (see below).

Reviews.
1. Perry CM, Wagstaff AJ. Famciclovir: a review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. *Drugs* 1995; **50:** 396–415.
2. Faro S. A review of famciclovir in the management of genital herpes. *Infect Dis Obstet Gynecol* 1998; **6:** 38–43.
3. Vinh DC, Aoki FY. Famciclovir for the treatment of recurrent genital herpes: a clinical and pharmacological perspective. *Expert Opin Pharmacother* 2006; **7:** 2271–86.
4. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006; **66:** 2397–2416.
5. Chacko M, Weinberg JM. Famciclovir for cutaneous herpesvirus infections: an update and review of new single-day dosing indications. *Cutis* 2007; **80:** 77–81.
6. Aoki FY. The continuing evolution of antiviral therapy for recurrent genital herpes: 1-day patient-initiated treatment with famciclovir. *Herpes* 2007; **14:** 62–5.
7. Mubareka S, *et al.* Famciclovir: a focus on efficacy and safety. *Expert Opin Drug Safety* 2010; **9:** 643–58.

Administration in renal impairment. Doses of famciclovir need to be reduced in patients with renal impairment. The following oral doses based on creatinine clearance (CC) are recommended:

Immunocompetent patients:

Herpes zoster
- CC 40 to 59 mL/minute: 500 mg twice daily for 7 days
- CC 20 to 39 mL/minute: 500 mg once daily for 7 days
- CC < 20 mL/minute: 250 mg once daily for 7 days
- patients on haemodialysis: 250 mg is given immediately after each dialysis run during 7 days

Initial episode of genital herpes
- CC 20 to 39 mL/minute: 250 mg twice daily for 5 days
- CC < 20 mL/minute: 250 mg once daily for 5 days
- patients on haemodialysis: 250 mg is given immediately after each dialysis run during 5 days

Acute recurrent genital herpes, treatment
- CC ≥ 20 mL/minute: 125 mg twice daily for 5 days
- CC < 20 mL/minute: 125 mg once daily for 5 days
- patients on haemodialysis: 125 mg is given immediately after each dialysis run during 5 days

Recurrent genital herpes, suppression
- CC 20 to 39 mL/minute: 125 mg twice daily
- CC < 20 mL/minute: 125 mg once daily
- patients on haemodialysis: 125 mg is given immediately after each dialysis run

For single-day dose regimens for recurrent genital herpes
- 40 to 59 mL/minute: 500 mg every 12 hours for 1 day
- 20 to 39 mL/minute: 500 mg as a single dose
- < 20 mL/minute: 250 mg as a single dose
- patients on haemodialysis: 250 mg is given immediately after the dialysis run

For single-dose treatment for recurrent herpes labialis
- 40 to 59 mL/minute: 750 mg as a single dose
- 20 to 39 mL/minute: 500 mg as a single dose
- < 20 mL/minute: 250 mg as a single dose
- patients on haemodialysis: 250 mg is given immediately after the dialysis run

Immunocompromised patients:

Herpes zoster
- as for immunocompetent patients, above, but treatment is given for 10 days

Acute recurrent genital or orofacial herpes, treatment
- CC 20 to 39 mL/minute: 500 mg once daily for 7 days
- CC < 20 mL/minute: 250 mg once daily for 7 days
- patients on haemodialysis: 250 mg is given immediately after each dialysis run during 7 days

Recurrent genital herpes, suppression
- CC 20 to 39 mL/minute: 500 mg once daily
- CC < 20 mL/minute: 250 mg once daily
- patients on haemodialysis: 250 mg is given immediately after each dialysis run

Adverse Effects and Precautions

The most common adverse effects of famciclovir are headache and nausea. Other adverse effects rarely reported include jaundice, vomiting, dizziness, rash, pruritus, urticaria, somnolence, confusion, thrombocytopenia, and hallucinations. In addition, abdominal pain and fever have been reported in immunocompromised patients given famciclovir. There have been case reports of serious skin reactions such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Dosage should be reduced in patients with renal impairment. Acute renal failure has occurred in patients with renal impairment taking inappropriately high doses of famciclovir.

References.
1. Saltzman R, *et al.* Safety of famciclovir in patients with herpes zoster and genital herpes. *Antimicrob Agents Chemother* 1994; **38:** 2454–7.

Hypersensitivity. See Vasculitis, below. For conflicting findings regarding cross-sensitivity to famciclovir in patients hypersensitive to aciclovir, see p. 965.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies famciclovir as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Pregnancy. For information on the use of famciclovir in pregnancy see under Precautions of Aciclovir, p. 965.3.

Vasculitis. Leucocytoclastic (or hypersensitivity) vasculitis, a type of cutaneous small vessel vasculitis, occurred in an elderly woman 3 days after starting famciclovir 500 mg orally 3 times daily for treatment of shingles;[1] symptoms improved after about 2 months with oral corticosteroid treatment. The report authors identified famciclovir as the most likely cause, and based on a previous case report,[2] suggested that the risk of reaction may be dose dependent.

1. Te CC, *et al.* Famciclovir-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2008; **42:** 1323–6.
2. Ali SO, *et al.* Case reports: cutaneous small vessel vasculitis due to famciclovir therapy. *J Drugs Dermatol* 2005; **4:** 486–9.

Interactions

When given with famciclovir, probenecid may reduce renal excretion of the active metabolite penciclovir, leading to increased plasma concentrations. The conversion of famciclovir to penciclovir is, in part, mediated by aldehyde oxidase, and strong inhibitors of this enzyme (such as raloxifene) may potentially reduce the formation of penciclovir.

Antiviral Action

As for Penciclovir, p. 1008.3.

Pharmacokinetics

Famciclovir is rapidly absorbed after oral doses. Absorption is delayed but not reduced by food. Famciclovir is rapidly converted to penciclovir (see p. 1008.3) and peak plasma concentrations occur within about 1 hour of a dose; virtually no famciclovir is detectable in the plasma or urine. Bioavailability of penciclovir is reported to be 77%. Famciclovir is mainly excreted in the urine (partly by renal tubular secretion) as penciclovir and its 6-deoxy precursor; elimination is reduced in patients with renal impairment.

References.
1. Pue MA, Benet LZ. Pharmacokinetics of famciclovir in man. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 47–55.
2. Boike SC, *et al.* Pharmacokinetics of famciclovir in subjects with varying degrees of renal impairment. *Clin Pharmacol Ther* 1994; **55:** 418–26.
3. Boike SC, *et al.* Pharmacokinetics of famciclovir in subjects with chronic hepatic disease. *J Clin Pharmacol* 1994; **34:** 1199–1207.
4. Gill KS, Wood MJ. The clinical pharmacokinetics of famciclovir. *Clin Pharmacokinet* 1996; **31:** 1–8.
5. Sáez-Llorens X, *et al.* Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. *Antimicrob Agents Chemother* 2009; **53:** 1912–20.
6. Ogungbenro K, *et al.* Population pharmacokinetics and optimal design of paediatric studies for famciclovir. *Br J Clin Pharmacol* 2009; **68:** 546–60.
7. Blumer J, *et al.* Single-dose pharmacokinetics of famciclovir in infants and population pharmacokinetic analysis in infants and children. *Antimicrob Agents Chemother* 2010; **54:** 2032–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pentavir; ***Austral.***: Ezovir; Famvir; Favic; ***Austria***: Famvir; ***Braz.***: Famvir; Fanclomax; Penvir; ***Canad.***: Famvir; ***China***: Fanle (凡乐); Lizhufeng (丽珠风); Ming Li Xin (明立欣); Nuo Ke (诺克); Pixin (彼欣); Wan Qi (万祺); Weike (韦克); Xian Lin Na (仙林纳); ***Cz.***: Famvir†; ***Denm.***:

The symbol † denotes a preparation no longer actively marketed

Famvir; *Fin.*: Famvir; *Fr.*: Oravir; *Ger.*: Famvir; *Gr.*: Famcilet; Famvir; *Hong Kong*: Famvir; *Hung.*: Famvir; *India*: Famirax; Famtrex; Microvir; *Indon.*: Famvir; *Irl.*: Famlov; Famvir; Mycloveart†; *Ital.*: Famvir; Ziravir†; *Jpn*: Famvir; *Neth.*: Famvir†; *NZ*: Famvir; *Port.*: Famvir†; Zyvir†; *Rus.*: Famvir (Фамвир); *S.Afr.*: Famvir; *Spain*: Ancivin†; Famvir; *Swed.*: Famvir; *Switz.*: Famvir; *Thai.*: Famvir; *Turk.*: Famvir; *UK*: Famvir; *Ukr.*: Famvir (Фамвир); *USA*: Famvir.

Fomivirsen Sodium *(BANM, USAN, rINNM)*

Fomivirseeninatrium; Fomivirsén sódico; Fomivirsen Sodique; Fomivirsennatrium; Fomivirseno sódico; Fomivirsenum Natricum; Isis-2922; Natrii Fomivirsenum; Натрий Фомивирсен.

$C_{204}H_{243}N_{63}Na_{20}O_{114}P_{20}S_{20}$=7122.0

CAS — 144245-52-3 (fomivirsen); 160369-77-7 (fomivirsen sodium).

ATC — S01AD08.

ATC Vet — QS01AD08.

UNII — 3Z6W3536X5.

Uses and Administration

Fomivirsen is an antisense oligonucleotide that has been used as the sodium salt for the local treatment of CMV retinitis (p. 954.2) in patients with AIDS. For newly diagnosed disease, a dose of 165 micrograms has been given by intravitreal injection into the affected eye once each week for 3 weeks, then on alternate weeks thereafter. For previously treated disease, 330 micrograms has been injected into the affected eye; this dose may be repeated once after 2 weeks and then once every 4 weeks thereafter.

Reviews.

1. Perry CM, Barman Balfour JA. Fomivirsen. *Drugs* 1999; 57: 375–80.
2. Geary RS, *et al.* Fomivirsen: clinical pharmacology and potential drug interactions. *Clin Pharmacokinet* 2002; 41: 255–60.

Adverse Effects and Precautions

Adverse effects after intra-ocular injection of fomivirsen are confined to the treated eye. They include intra-ocular inflammation, transient increases in intra-ocular pressure, retinal detachment and oedema, and visual abnormalities. Other adverse effects associated with the intravitreal injection procedure include vitreal haemorrhage, endophthalmitis, uveitis, and cataract formation.

Patients should be monitored during treatment for changes in intra-ocular pressure and visual field and for extra-ocular CMV disease or disease in the contralateral eye.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fomivirsen as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Interactions

In order to reduce the risk of inflammation, intra-ocular use of fomivirsen is not recommended within 2 to 4 weeks of cidofovir treatment.

Antiviral Action

Fomivirsen is an antisense oligonucleotide that inhibits human CMV replication. It is active against strains of CMV resistant to ganciclovir, foscarnet, and cidofovir. Resistance to fomivirsen has been induced *in vitro*, but cross-resistance to antivirals with other modes of action is unlikely.

Fosamprenavir Calcium *(USAN, rINNM)*

Calcii Fosamprenavirum; Fosamprenavir cálcico; Fosamprénavir Calcique; GW-433908G; Кальций Фосампренавир.

(3*S*)-Tetrahydro-3-furyl[(α*S*)-α-[(1*R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl]carbamate calcium phosphate (1:1)

$C_{25}H_{36}CaN_3O_9PS$=625.7

CAS — 226700-79-4 (fosamprenavir); 226700-81-8 (fosamprenavir calcium).

ATC — J05AE07.

ATC Vet — QJ05AE07.

UNII — ID1GU2627N.

Uses and Administration

Fosamprenavir is a prodrug of amprenavir, which is an HIV-protease inhibitor with antiviral activity against HIV. Fosamprenavir is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when fosamprenavir is used alone, and it is therefore used with other antiretrovirals.

Fosamprenavir may be given with or without food. It is given orally as the calcium salt, but doses are expressed in terms of the base. Fosamprenavir calcium 748 mg is equivalent to about 700 mg of fosamprenavir. Licensed product information states that this is equivalent to about 600 mg of amprenavir.

In the UK, the recommended dose of ritonavir-boosted fosamprenavir in both treatment-experienced and treatment-naive adult patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

In the USA, recommended doses in treatment-naive adult patients are:

- fosamprenavir 1.4 g twice daily *without ritonavir*, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 200 mg once daily, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 100 mg once daily, or
- fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily

The recommended dose in treatment-experienced patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

For details of doses in children and adolescents, see below.

Doses should be reduced in patients with hepatic impairment (see below).

Reviews.

1. Chapman TM, *et al.* Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. *Drugs* 2004; 64: 2101–24.
2. Hester EK, *et al.* Fosamprenavir: drug development for adherence. *Ann Pharmacother* 2006; 40: 1301–10.
3. Torres HA, Arduino RC. Posamprenavir calcium plus ritonavir for HIV infection. *Expert Rev Anti Infect Ther* 2007; 5: 349–63.

Administration in children. For the treatment of HIV infection in children and adolescents, fosamprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight and totals should not exceed the adult dose (see Uses and Administration, above).

In the UK, the recommended dose of fosamprenavir oral solution in children and adolescents weighing 25 to 38 kg is 18 mg/kg twice daily *plus* ritonavir oral solution 3 mg/kg twice daily. Children and adolescents weighing at least 39 kg may be given the adult fosamprenavir tablet dose, see above. It is not licensed for use in children below 25 kg in weight or 6 years of age.

In the USA, fosamprenavir oral solution is licensed for use in infants born at 38-weeks gestation or greater and who are at least 28 days old. For the treatment of *protease inhibitor-naive* infants and children from 4 weeks of age and *protease inhibitor-experienced* infants and children from 6 months of age the recommended doses are:

- those weighing less than 11 kg: fosamprenavir 45 mg/kg twice daily plus ritonavir 7 mg/kg twice daily
- those weighing 11 to less than 15 kg: fosamprenavir 30 mg/kg twice daily plus ritonavir 3 mg/kg twice daily
- those weighing 15 to less than 20 kg: fosamprenavir 23 mg/kg twice daily plus ritonavir 3 mg/kg twice daily
- those weighing 20 kg or more: fosamprenavir 18 mg/kg twice daily plus ritonavir 3 mg/kg twice daily

Alternatively, *protease inhibitor-naive* children from 2 years of age may be given 30 mg/kg twice daily of fosamprenavir without ritonavir.

Ritonavir 100-mg capsules may be given to children and adolescents taking fosamprenavir oral suspension if they weigh at least 33 kg.

Administration in hepatic impairment. Fosamprenavir should be used with caution in all patients with hepatic impairment.

UK licensed product information recommends:

- in patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with severe hepatic impairment (Child-Pugh score 10 to 15): fosamprenavir 300 mg twice daily *plus* ritonavir 100 mg once daily

US licensed product information recommends:

- in treatment-naive patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *without ritonavir*, or *plus* ritonavir 100 mg once daily
- in HIV-protease inhibitor-experienced patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 700 mg twice daily *without ritonavir*, or fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in HIV-protease inhibitor-experienced patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with severe hepatic impairment (Child-Pugh score 10 to 15): fosamprenavir 350 mg twice daily *without ritonavir*, or fosamprenavir 300 mg twice daily *plus* ritonavir 100 mg once daily
- in protease-inhibitor experienced patients with severe hepatic impairment (Child-Pugh score 10 to 15): fosamprenavir 300 mg twice daily *plus* ritonavir 100 mg once daily

Adverse Effects

Adverse effects associated with antiretroviral regimens containing fosamprenavir or amprenavir are mostly mild to moderate. The most common adverse effects are gastrointestinal disturbances such as diarrhoea, flatulence, nausea and vomiting. Other commonly reported adverse effects include fatigue, headache, oral paraesthesia, and taste disorders, while the most frequently reported adverse effects include peripheral paraesthesias and mood disorders (including depression). Mild to moderate rashes (usually erythematous or maculopapular and sometimes pruritic), generally occur during the second week of treatment and resolve within 2 weeks. A possible association with Stevens-Johnson syndrome has been reported.

For further information on adverse effects associated with HIV-protease inhibitors, see under Indinavir Sulfate, p. 986.2

Precautions

Amprenavir or fosamprenavir should be used with caution (and liver enzyme values monitored), in patients with hepatic impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Treatment with amprenavir should be permanently stopped in patients who develop a severe or life-threatening rash or a rash with associated systemic or allergic symptoms or mucosal involvement.

Amprenavir is a sulfonamide and the drugs should be used with caution in patients known to be allergic to sulfonamides. For further information on cross-reactivity between sulfonamide drugs see Hypersensitivity, under Sulfamethoxazole, p. 365.3.

Interactions

Drugs interacting with amprenavir might reasonably also be expected to interact with fosamprenavir. Amprenavir is reported to be metabolised by the cytochrome P450 isoenzyme CYP3A4. It is also a modest inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that affect these isoenzymes may modify amprenavir plasma concentrations and amprenavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system.

Amprenavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergotamine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam) and statins (simvastatin and lovastatin). Similarly, ritonavir-boosted amprenavir should not be used with drugs having narrow therapeutic windows that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide and propafenone. Rifampicin and St John's wort decrease the concentration of amprenavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Fosamprenavir is a prodrug that is rapidly hydrolysed to amprenavir by cellular phosphatases in the gut epithelium as it is absorbed; it has little or no antiviral activity of its own *in vitro*. Amprenavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance between HIV-protease inhibitors may occur, but cross

resistance between HIV-protease inhibitors and reverse transcriptase inhibitors is considered unlikely. Mechanisms of resistance to amprenavir may differ from those of other HIV-protease inhibitors.

Pharmacokinetics

After oral doses, fosamprenavir is rapidly hydrolysed to amprenavir in the gastrointestinal epithelium as it is absorbed. Peak plasma concentrations of amprenavir occur after 1.5 to 4 hours. Fosamprenavir may be given with or without food. For details of the pharmacokinetics of amprenavir, see p. 968.1.

References.

1. Wire MB, *et al.* Fosamprenavir: clinical pharmacokinetics and drug interactions of the amprenavir prodrug. *Clin Pharmacokinet* 2006; **45**: 137–68.
2. Pérez-Elías MJ, *et al.* Pharmacokinetics of fosamprenavir plus ritonavir in human immunodeficiency virus type 1-infected adult subjects with hepatic impairment. *Antimicrob Agents Chemother* 2009; **53**: 5185–96.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Telzir; *Austral.*: Telzir; *Austria*: Telzir; *Belg.*: Telzir; *Braz.*: Telzir; *Canad.*: Telzir; *Chile*: Telzir; *Cz.*: Telzir; *Denm.*: Telzir; *Fin.*: Telzir; *Fr.*: Telzir; *Ger.*: Telzir; *Gr.*: Telzir; *Hung.*: Telzir; *Irl.*: Telzir; *Israel*: Lexiva; *Ital.*: Telzir; *Mex.*: Telzer; *Neth.*: Telzir; *Norw.*: Telzir; *Pol.*: Telzir; *Port.*: Telzir; *Rus.*: Telzir (Телзир); *Spain*: Telzir; *Swed.*: Telzir; *Switz.*: Telzir; *Turk.*: Telzir; *UK*: Telzir; *USA*: Lexiva.

Foscarnet Sodium *(BAN, USAN, rINN)*

A-29622; EHB-776 (anhydrous and hexahydrate); Foscarnet sódico; Foscarnet Sodique; Foscarnet sodique hexahydraté; Foscarnetum Natricum; Foscarnetum Natricum Hexahydricum; Foskarneettinatriumheksahydraatti; Foskarnet sodná sůl hexahydrát; Foskarnet Sodyum; Foskarnetnatriumhexahydrat; Foskarneto natrio druska heksahidratas; Foszkarnétnátrium; Phosphonatoformate Trisodium; Phosphonoformate Trisodium; Фоскарнет Натрий.

Trisodium phosphonatoformate hexahydrate.

$CNa_3O_5P,6H_2O=300.0$

CAS — 63585-09-1 (foscarnet sodium); 34156-56-4 (foscarnet sodium hexahydrate).

ATC — J05AD01.

ATC Vet — QJ05AD01.

UNII — 964YS0OOG1.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Foscarnet Sodium Hexahydrate; Foscarnet Sodium BP 2014). A white or almost white crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Protect from light.

USP 36: (Foscarnet Sodium). A white to almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Store in airtight containers. Protect from light.

Incompatibility. Foscarnet sodium has been found to be visually incompatible with some commonly used injectable drugs including amphotericin B, aciclovir sodium, cotrimoxazole, ganciclovir, and pentamidine isetionate;[1,2] licensed product information also lists incompatibilities with vancomycin, glucose 30% solution, and solutions containing calcium. It is therefore recommended that foscarnet should not be infused via an intravenous line with any other drug.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47**: 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47**: 2075–7.

Uses and Administration

Foscarnet is a non-nucleoside pyrophosphate analogue active against herpesviruses. It is used as the trisodium salt mainly for the treatment of CMV retinitis in AIDS patients (see below) and for aciclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients (see below).

Foscarnet is given by intravenous infusion. A solution containing foscarnet sodium 24 mg/mL may be given via a central vein or diluted with glucose 5% or sodium chloride 0.9% to a concentration of 12 mg/mL and given via a peripheral vein. Hydration with 0.5 to 1 litre of sodium chloride 0.9% is recommended with each infusion to reduce renal toxicity.

For the treatment of **CMV retinitis** in patients with normal renal function, the usual dose is 60 mg/kg infused over at least 1 hour every 8 hours, or 90 mg/kg infused over 1½ to 2 hours every 12 hours, for 2 to 3 weeks; this should then be followed by maintenance therapy with 60 mg/kg daily, increasing to 90 to 120 mg/kg daily infused over 2 hours if tolerated.

For the treatment of aciclovir-resistant mucocutaneous **herpes simplex virus infections** in patients with normal renal function, a dose of 40 mg/kg, infused over at least 1 hour every 8 or 12 hours is given for 2 to 3 weeks or until lesions have healed.

Doses of foscarnet should be reduced in patients with renal impairment (see below).

Reviews.

1. Chrisp P, Clissold SP. Foscarnet: a review of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. *Drugs* 1991; **41**: 104–29.
2. Wagstaff AJ, Bryson HM. Foscarnet: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs* 1994; **48**: 199–226.

Administration in children. Foscarnet is not licensed for use in children in the UK. However, the *BNFC* considers that it may be used if necessary for CMV disease or mucocutaneous herpes simplex infection in children from 1 month of age. For CMV infection, foscarnet may be given in an induction dose of 60 mg/kg by intravenous infusion every 8 hours for 2 to 3 weeks, followed by maintenance in similar doses to those recommended for adults with CMV retinitis (see Uses and Administration, above). For mucocutaneous herpes simplex it recommends 40 mg/kg given every 8 hours for 2 to 3 weeks, or until lesions heal.

Administration in renal impairment. Doses of intravenous foscarnet sodium may need to be reduced in patients with renal impairment.

Treatment of CMV retinitis:

The following doses, given every 8 hours for treatment and once daily for maintenance, are suggested by the UK licensed product information according to creatinine clearance (CC):

- CC more than 1.6 mL/kg per minute: 60 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 55 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 49 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 42 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 35 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 28 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 21 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

Treatment of aciclovir-resistant mucocutaneous herpes simplex infections:

The following doses, given every 8 hours, are suggested by the UK licensed product information according to CC:

- CC more than 1.6 mL/kg per minute: 40 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 37 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 33 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 28 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 24 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 19 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 14 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

In the USA modification of doses by extending the dose interval has been recommended, resulting in proportional reductions in daily dose similar to those in the UK.

Cytomegalovirus infections. Foscarnet is used in the treatment of severe CMV infections (p. 954.2) in immunocompromised patients and appears to possess similar efficacy to ganciclovir[1] (see also under Ganciclovir, p. 983.1). It has been particularly useful in patients who require antiretroviral therapy for AIDS and are unable to tolerate ganciclovir (because of haematological toxicity). For patients unable to tolerate systemic therapy foscarnet has been tried as an intravitreal injection.[2–4] Beneficial responses have been reported with various regimens including intravitreal injections of foscarnet 1.2 mg every 48 hours for 4 doses[2] or induction with 2.4 mg twice weekly[4] or every 72 hours for 6 doses,[3] then once weekly maintenance thereafter.[3,4] Combined treatment with foscarnet and ganciclovir each given intravitreally has also been reported to be effective;[5] however, although combination systemic therapy has been widely used where resistance to ganciclovir is suspected, the evidence for a synergistic effect against CMV is not very strong.[6]

Foscarnet has also been investigated for primary prophylaxis of CMV infection in bone marrow transplant recipients at high risk of infection.[7,8]

1. Reusser P, *et al.* Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood* 2002; **99**: 1159–64.
2. Lieberman RM, *et al.* Efficacy of intravitreal foscarnet in a patient with AIDS. *N Engl J Med* 1994; **330**: 868–9.
3. Díaz-Llopis M, *et al.* High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS. *Br J Ophthalmol* 1994; **78**: 120–4.
4. Ausayakhun S, *et al.* Intravitreal foscarnet for cytomegalovirus retinitis in patients with AIDS. *J Med Assoc Thai* 2005; **88**: 103–7.
5. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131**: 396–7.
6. Drew WL. Is combination antiviral therapy for CMV superior to monotherapy? *J Clin Virol* 2006; **35**: 485–8.
7. Ippoliti C, *et al.* Foscarnet for prevention of cytomegalovirus infection in allogeneic marrow transplant recipients unable to receive ganciclovir. *Bone Marrow Transplant* 1997; **20**: 491–5.
8. Bregante S, *et al.* Foscarnet prophylaxis of cytomegalovirus infections in patients undergoing allogeneic bone marrow transplantation (BMT): a dose-finding study. *Bone Marrow Transplant* 2000; **26**: 23–9.

Herpes simplex infections. Although foscarnet is effective in the treatment of herpes simplex infections it is usually reserved for severe or disseminated herpes simplex infections, particularly in immunocompromised patients who have infections resistant to aciclovir (see p. 955.2). A 2% cream applied topically is effective in the treatment of refractory herpes simplex infections of the skin,[1] and is licensed for such use in some countries. Topical use of a 1% foscarnet cream has also been investigated.[2] For mention of intravitreal foscarnet in the management of herpes-simplex-induced acute retinal necrosis see under Varicella-zoster Infections, below.

1. Gross G, Braun D. Wirksamkeit und Verträglichkeit von topisch applizierterm Foscarnet-Natrium bei der Behandlung von Herpes labialis. Ergebnisse einer Anwendungsbeobachtung. *Hautarzt* 2006; **57**: 40–6.
2. Javaly K, *et al.* Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr* 1999; **21**: 301–6.

HIV infection. Foscarnet has some activity against HIV reverse transcriptase and in patients with HIV infection (p. 957.2) that has become resistant to multiple antiretrovirals, it has been investigated[1–3] in salvage regimens; there is some evidence that response depends on the number and nature of any thymidine-associated mutations present in the virus.

1. Canestri A, *et al.* Foscarnet salvage therapy for patients with late-stage HIV disease and multiple drug resistance. *Antivir Ther* 2006; **11**: 561–6.
2. Mathiesen S, *et al.* Long-term foscarnet therapy remodels thymidine analogue mutations and alters resistance to zidovudine and lamivudine in HIV-1. *Antivir Ther* 2007; **12**: 335–43.
3. Charpentier C, *et al.* Foscarnet salvage therapy efficacy is associated with the presence of thymidine-associated mutations (TAMs) in HIV-infected patients. *J Clin Virol* 2008; **43**: 212–5.

Varicella-zoster infections. Intravenous foscarnet is the recommended treatment for aciclovir-resistant varicella-zoster infections (p. 956.2). In a study[1] of 5 patients with AIDS and aciclovir-resistant zoster infection complete healing was reported for 3 patients after treatment with foscarnet 120 mg/kg daily for 14 to 26 days. Two patients relapsed 7 and 14 days respectively after stopping treatment. In another study[2] 10 of 13 HIV-infected patients with aciclovir-resistant zoster infection had complete healing after treatment with 100 mg/kg twice daily of foscarnet for 12 to 30 days. Five of the patients relapsed after stopping treatment with the median time to relapse being 110 days. Intravitreal foscarnet has been suggested as a useful adjunct in preventing retinal detachment in patients with varicella-zoster-induced acute retinal necrosis; it was unclear if it was of similar value in those with herpes-simplex-induced disease.[3]

1. Safrin S, *et al.* Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann Intern Med* 1991; **115**: 19–21.
2. Breton G, *et al.* Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis* 1998; **27**: 1525–7.
3. Wong R, *et al.* Acute retinal necrosis: the effects of intravitreal foscarnet and virus type on outcome. *Ophthalmology* 2010; **117**: 556–60.

Adverse Effects and Treatment

The most serious common adverse effect of foscarnet sodium is renal impairment, which may be severe. Anaemia may be common and granulocytopenia and thrombocytopenia have been reported. Foscarnet can chelate bivalent metal ions, and may be associated with an acute decrease in ionised calcium in the plasma that is not necessarily reflected by measurements of total calcium; the decrease is proportional to the rate of infusion. Other electrolyte disturbances may occur (see p. 982.1). Some patients may have convulsions. Excretion of high concentrations in the urine can cause local irritation and genital ulceration. Other adverse effects reported include nausea, vomiting, diarrhoea, malaise, fatigue, fever, headache, dizziness, paraesthesia, tremor, mood disturbances, rash, abnormal liver function tests, blood pressure and ECG changes, and isolated reports of pancreatitis. Intravenous injection may cause phlebitis at the site of injection.

In cases of overdosage it is important to maintain hydration. Foscarnet elimination may be increased by haemodialysis.

Effects on the CNS. Convulsions may occur in up to 10% of AIDS patients receiving foscarnet and have been reported after overdoses. Contributing factors include underlying CNS pathology (HIV-related encephalopathy or other infections) and foscarnet-related electrolyte disturbances. However, seizures have occurred in patients without apparent risk factors.[1]

An acute dystonic reaction has also been reported[2] in a patient treated with foscarnet.

1. Lor E, Liu YQ. Neurologic sequelae associated with foscarnet therapy. *Ann Pharmacother* 1994; 28: 1035–7.
2. Dubow JS, *et al.* Acute dystonic reaction associated with foscarnet administration. *Am J Ther* 2008; 15: 184–6.

Effects on electrolyte balance. Acute hypocalcaemia has been reported to occur in about 30% of AIDS patients receiving foscarnet. Other electrolyte disturbances include hypokalaemia and hypomagnesaemia (each in about 15%), hypophosphataemia (8%), and hyperphosphataemia (6%). Hypocalcaemia may cause paraesthesias and, together with hypomagnesaemia and hypokalaemia, may predispose to seizures and cardiovascular disturbances.

Electrolyte abnormalities (increased calcium, magnesium, phosphate, and potassium requirements, and a reduction in the need for sodium) have been reported to be dramatically accelerated by foscarnet in a patient being given total parenteral nutrition.[1]

1. Matarese LE, *et al.* Foscarnet-induced electrolyte abnormalities in a bone marrow transplant patient receiving parenteral nutrition. *J Parenter Enteral Nutr* 2000; 24: 170–3.

Effects on the kidneys. The most serious common adverse effect of foscarnet sodium is nephrotoxicity. Clinically significant increases in serum-creatinine concentrations occur in about 30% of patients, and the incidence of nephrotoxicity tends to increase with increasing dose[1] and with duration of therapy.[2] Foscarnet sodium is excreted unchanged in the urine and tubulo-interstitial lesions and deposition of crystals in the glomerular capillary lumen have been implicated.[3] Acute renal failure has occurred and haemodialysis has been reported to have reduced plasma-foscarnet concentrations.[4] The risk of nephrotoxicity can be minimised by ensuring adequate hydration, the use of intermittent dosing schedules,[5] and by adjusting the dose according to serum-creatinine concentrations. Nephrogenic diabetes insipidus and renal tubular acidosis associated with foscarnet have been reported.[6-8]

1. Jacobson MA, *et al.* A dose-ranging study of daily maintenance intravenous foscarnet therapy for cytomegalovirus retinitis in AIDS. *J Infect Dis* 1993; 168: 444–8.
2. Gaub J, *et al.* The effect of foscarnet (phosphonoformate) on human immunodeficiency virus isolation, T-cell subsets and lymphocyte function in AIDS patients. *AIDS* 1987; 1: 27–33.
3. Beaufils H, *et al.* Foscarnet and crystals in glomerular capillary lumens. *Lancet* 1990; 336: 755.
4. Deray G, *et al.* Foscarnet-induced acute renal failure and effectiveness of haemodialysis. *Lancet* 1987; ii: 216.
5. Deray G, *et al.* Prevention of foscarnet nephrotoxicity. *Ann Intern Med* 1990; 113: 332.
6. Parese RV, *et al.* Nephrogenic diabetes insipidus associated with foscarnet treatment of cytomegalovirus retinitis. *Ann Intern Med* 1990; 112: 955–6.
7. Conn J, *et al.* Nephrogenic diabetes insipidus associated with foscarnet—a case report. *J Antimicrob Chemother* 1996; 37: 1180–1.
8. Navarro JF, *et al.* Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996; 27: 431–4.

Effects on the skin and mucous membranes. A generalised pruritic macular rash was reported in a patient given foscarnet, which subsided after the drug was withdrawn.[1]

There have been several reports of genital ulceration,[2-8] possibly related to local toxicity arising from high concentrations of foscarnet in the urine. Oral ulceration, usually with genital ulceration, has occurred during foscarnet treatment.[3-5] Uvular and oesophageal ulcerations have also been reported.[4,9]

1. Green ST, *et al.* Generalised cutaneous rash associated with foscarnet usage in AIDS. *J Infect* 1990; 21: 227–8.
2. Van Der Pijl JW, *et al.* Foscarnet and penile ulceration. *Lancet* 1990; 335: 286.
3. Gilquin J, *et al.* Genital and oral erosions induced by foscarnet. *Lancet* 1990; 335: 287.
4. Fégueux S, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; 335: 547.
5. Moyle G, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; 335: 547–8.
6. Lacey HB, *et al.* Vulval ulceration associated with foscarnet. *Genitourin Med* 1992; 68: 182.
7. Caumes E, *et al.* Foscarnet-induced vulvar erosion. *J Am Acad Dermatol* 1993; 28: 799.
8. Elck RW, Prose N. Penile erosions associated with foscarnet therapy in a child. *Pediatr Dermatol* 2010; 27: 302–3.
9. Saint-Marc T, *et al.* Uvula and oesophageal ulcerations with foscarnet. *Lancet* 1992; 340: 970–1.

Precautions

Foscarnet sodium should be used with caution in renal impairment and doses should be reduced if serum creatinine is raised. Serum-creatinine concentrations should be measured on alternate days throughout induction treatment; monitoring may be weekly during maintenance therapy. An adequate state of hydration must be maintained during therapy to prevent renal toxicity. Electrolytes, especially calcium and magnesium, should also be monitored and deficiencies corrected before and during foscarnet therapy.

Electrolyte content. Each g of foscarnet sodium (hexahydrate) contains about 10 mmol of sodium and about 3.3 mmol of phosphate.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies foscarnet as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Interactions

Foscarnet should not be given with other nephrotoxic drugs such as aminoglycosides, amphotericin B, and ciclosporin, or with other drugs that can affect serum-calcium concentrations. Intravenous pentamidine can produce both of these effects and severe additive toxicity may result from its use with foscarnet; fatalities have occurred.

Ciprofloxacin. Tonic-clonic seizures associated with foscarnet use in 2 patients receiving multiple antimicrobial drugs were thought to have been exacerbated by the concurrent use of ciprofloxacin.[1]

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; 28: 869–72.

Parenteral nutrition. For mention that foscarnet may exacerbate the need for electrolyte replacement in patients receiving total parenteral nutrition see Effects on Electrolyte Balance, above.

Antiviral Action

Foscarnet inhibits replication of human herpesviruses including CMV, herpes simplex virus types 1 and 2, herpesviruses 6 and 8, Epstein-Barr virus, and varicella-zoster virus. Activity is also reported against hepatitis B virus and HIV. Foscarnet acts by inhibition of virus-specific DNA polymerases and reverse transcriptases: unlike the nucleoside reverse transcriptase inhibitors and ganciclovir, foscarnet does not require intracellular conversion to an active triphosphate.

References.

1. Balfour HH, *et al.* Effect of foscarnet on quantities of cytomegalovirus and human immunodeficiency virus in blood of persons with AIDS. *Antimicrob Agents Chemother* 1996; 40: 2721–6.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; 42: 2240–4.

Pharmacokinetics

The pharmacokinetics of foscarnet are complicated by the high incidence of renal impairment induced during therapy and by the deposition and subsequent gradual release of foscarnet from bone. Thus the estimation of half-life depends upon the duration of foscarnet therapy and the duration of the observation period. The plasma half-life in patients with normal renal function is about 2 to 4 hours, but terminal half-lives up to about 8 days have been reported when accumulation in bone has taken place. Plasma protein binding is about 14 to 17%. Foscarnet crosses the blood-brain barrier in variable amounts; CSF concentrations ranging from zero to more than 3 times the plasma concentration have been reported. Foscarnet is mostly excreted unchanged in the urine mainly through glomerular filtration.

In 13 HIV-infected male patients with lymphadenopathy or AIDS-related complex[1] foscarnet [sodium] by continuous intravenous infusion (140 to 190 micrograms/kg per minute) produced plasma-foscarnet concentrations of about 100 to 500 nanomol/mL. There appeared to be a link between the degree of adverse effects and plasma-foscarnet concentrations above 350 nanomol/mL. Foscarnet was excreted mainly via the kidneys. It was thought that up to 20% of the cumulative intravenous dose may have been deposited in bone 7 days after the end of infusion.

Penetration of foscarnet into the CSF is very variable and in 5 patients[1] CSF concentrations of foscarnet were found to be 13 to 68% of those in the plasma. Subsequent studies showed that CSF concentrations of foscarnet would be virostatic in most patients,[2] attaining a mean concentration of about 25% of plasma concentration after a single infusion[2,3] and 66% under steady state conditions.[3] CSF concentrations ranged from 0 to 340%[2] and 5 to 72%[3] of those in plasma. There was a correlation between the amount of foscarnet in the CSF and inflammation of the meninges in one study,[2] and with the HIV infection stage in another,[3] but neither reported a correlation with plasma concentration.

1. Sjövall J, *et al.* Pharmacokinetics of foscarnet and distribution to cerebrospinal fluid after intravenous infusion in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1989; 33: 1023–31.
2. Raffi F, *et al.* Penetration of foscarnet into cerebrospinal fluid of AIDS patients. *Antimicrob Agents Chemother* 1993; 37: 1777–80.
3. Hengge UR, *et al.* Foscarnet penetrates the blood-brain barrier: rationale for therapy of cytomegalovirus encephalitis. *Antimicrob Agents Chemother* 1993; 37: 1010–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Foscavir; ***Belg.***: Foscavir; ***Braz.***: Foscavir; ***China***: Anji (安济); Carnet (可耐); Fu Shi Ling (扶适灵); Ka Nai Xin (卡奈信); Yi Ke Ya (易可亚); ***Fr.***: Foscavir; ***Ger.***: Foscavir†; Triapten; ***Gr.***: Foscavir; ***Hung.***: Foscavir; ***Israel***: Foscavir; ***Ital.***: Foscavir; ***Jpn***: Foscavir; ***Neth.***: Foscavir; ***Norw.***: Foscavir†; ***NZ***: Foscavir; ***Port.***: Foscavir; ***Singapore***: Foscavir; ***Spain***: Foscavir; ***Swed.***: Foscavir; ***Switz.***: Foscavir; ***UK***: Foscavir; ***USA***: Foscavir.

Pharmacopoeial Preparations
BP 2014: Foscarnet Infusion.

Ganciclovir *(BAN, USAN, rINN)*

BIOLF-62; BN-B759V; BW-759; BW-759U; BWB-759U; DHPG; 9-(1,3-Dihydroxy-2-propoxymethyl)guanine; Dihydroxypropoxymethylguanine; Ganciclovirum; Gancyklovir; Gancyklowir; Gansikloviri; Gansiklovir; RS-21592; Ганцикловир; 2'-NDG; 2'-Nor-2'-deoxyguanosine.

9-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine.

$C_9H_{13}N_5O_4$=255.2

CAS — 82410-32-0.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

UNII — P9G3CKZ4P5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Ganciclovir). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; very slightly soluble in alcohol; dissolves in dilute solutions of mineral acids and alkali hydroxides. Store in airtight containers.

USP 36: (Ganciclovir). A white to off-white crystalline powder. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Ganciclovir Sodium *(BANM, USAN, rINNM)*

Ganciclovir sódico; Ganciclovir Sodique; Natrii Ganciclovirum; Натрий Ганцикловир.

$C_9H_{12}N_5NaO_4$=277.2

CAS — 107910-75-8.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

UNII — 02L083W284.

Incompatibility. Ganciclovir is reported to be incompatible with foscarnet.

Stability. Ganciclovir sodium solution in sodium chloride 0.9% was found[1] to be stable when stored in polypropylene infusion-pump syringes for 12 hours at 25 degrees and for 10 days at 4 degrees. Little variation was found in ganciclovir concentration after storage of a 2% solution at room temperature, 5 degrees, and -8 degrees for 10 to 24 days.[2]

1. Mulye NV, *et al.* Stability of ganciclovir sodium in an infusion-pump syringe. *Am J Hosp Pharm* 1994; 51: 1348–9.
2. Morlet N, *et al.* High dose intravitreal ganciclovir for CMV retinitis: a shelf life and cost comparison study. *Br J Ophthalmol* 1995; 79: 753–5.

Uses and Administration

Ganciclovir is a synthetic nucleoside analogue of guanine closely related to aciclovir (p. 964.1), but has greater activity against CMV. It is used for the treatment and suppression of life-threatening or sight-threatening CMV infections in immunocompromised patients, including those with AIDS and those with iatrogenic immunosuppression associated with organ transplantation or chemotherapy of neoplastic disease (see also p. 983.1). It has also been used for superficial ocular herpes simplex infections.

Ganciclovir is given by intravenous infusion as the sodium salt but doses are expressed in terms of ganciclovir; 54.3 mg of ganciclovir sodium is equivalent to about 50 mg of ganciclovir. Solutions for infusion are usually prepared to give a concentration of ganciclovir of 50 mg/mL, then further diluted to contain not more than 10 mg/mL. An intravenous solution is given over 1 hour.

In **CMV infections**, the usual initial dose for ***treatment*** is 5 mg/kg by intravenous infusion every 12 hours for 14 to 21 days. This induction period may be followed by ***maintenance*** therapy to prevent recurrence or progression of the disease. The usual maintenance dosage is 5 mg/kg by intravenous infusion as a single daily dose for 7 days each week or 6 mg/kg daily for 5 days each week. If retinitis recurs or progresses a further induction course of ganciclovir may be given. AIDS patients who have received initial treatment with intravenous ganciclovir, and who have stable CMV retinitis following at least 3 weeks of intravenous therapy, may be given oral valganciclovir. In

some countries oral formulations of ganciclovir are available for maintenance; typical dosage is 3 g daily in divided doses.

For *prevention* of CMV infection in immunocompromised patients, specifically those receiving immunosuppressive therapy after organ transplantation, ganciclovir may be given in an *initial* dose of 5 mg/kg by intravenous infusion every 12 hours for 7 to 14 days, followed by intravenous *maintenance* therapy as above.

Doses of ganciclovir should be reduced in renal impairment (see below).

Intravitreal implants providing controlled release of ganciclovir are available for those patients with CMV retinitis who are unable to tolerate systemic therapy; the implants are designed to release ganciclovir over a period of 5 to 8 months.

Ganciclovir is also used as a topical ophthalmic 0.15% gel for the treatment of acute herpes simplex keratitis; the gel is usually applied 5 times daily until corneal healing occurs, then 3 times daily for a further 7 days.

For doses in children, see below.

General references.

1. Faulds D, Heel RC. Ganciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs* 1990; 39: 597–638.
2. Markham A, Faulds D. Ganciclovir: an update of its therapeutic use in cytomegalovirus infection. *Drugs* 1994; 48: 455–84.
3. Crumpacker CS. Ganciclovir. *N Engl J Med* 1996; 335: 721–9.
4. McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 2001; 61: 1153–83.

Administration in children. Ganciclovir is not licensed for use in children in the UK. However, the *BNFC* considers that it may be given for prevention or treatment of CMV infections in children from 1 month of age when necessary, in doses equivalent to those in adults (p. 982.3). For congenital CMV infection of the CNS in neonates a dose of 6 mg/kg by intravenous infusion every 12 hours is recommended, for a total of 6 weeks.

Administration in renal impairment. Doses of ganciclovir should be reduced in renal impairment. Licensed product information recommends the following intravenous doses based on creatinine clearance (CC):

- CC 70 mL/minute or more: 5 mg/kg every 12 hours for induction, followed by 5 mg/kg every 24 hours for maintenance
- CC 50 to 69 mL/minute: 2.5 mg/kg every 12 hours for induction, 2.5 mg/kg every 24 hours for maintenance
- CC 25 to 49 mL/minute: 2.5 mg/kg every 24 hours for induction, 1.25 mg/kg every 24 hours for maintenance
- CC 10 to 24 mL/minute: 1.25 mg/kg every 24 hours for induction, 625 micrograms/kg every 24 hours for maintenance
- dialysis patients: on days when dialysis is performed 1.25 mg/kg for induction, or 625 micrograms/kg for maintenance, in each case given shortly after the end of dialysis. In the USA, a maximum of 3 doses each week is recommended

For critically ill patients with CMV infection who are undergoing continuous renal replacement therapy, the following doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 2.5 mg/kg (induction) or 1.25 mg/kg (maintenance) every 24 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 2.5 mg/kg every 12 hours for induction or every 24 hours for maintenance

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Cytomegalovirus infections. Ganciclovir is used in both the treatment and prophylaxis of CMV infections (p. 954.2) in immunocompromised patients although the prodrug valganciclovir, which is as effective as ganciclovir and has a more convenient oral dosage regimen, may now be preferred.

As with other herpesvirus infections, antiviral treatment tends to be suppressive rather than curative, and long-term maintenance therapy is necessary. Treatment in patients with AIDS is complicated by the additive haematological toxicity of ganciclovir and zidovudine. Clinical studies comparing ganciclovir with foscarnet for AIDS-related CMV retinopathy have shown higher mortality rates in patients given ganciclovir than in those given foscarnet.[1,2] The use of ganciclovir with CMV immunoglobulins[3,4] or normal immunoglobulins,[5] or with foscarnet[6,7] has been reported to improve both efficacy and tolerance.

An alternative is the use of *intravitreal* controlled-release ganciclovir implants[8-11] to avoid systemic adverse effects. Intravitreal ganciclovir used with intravitreal foscarnet has been reported to be effective.[12]

Oral preparations of ganciclovir have been tried for maintenance therapy and may be a useful adjunct to prevent systemic infection in patients treated with the intravitreal implants[13] (but see under Resistance, p. 984.2). The use of oral ganciclovir in high doses has been investigated;[14] daily doses of up to 6 g have been reported to be of benefit, although a conclusive comparison with standard intravenous doses could not be made. CMV infections at other sites in AIDS patients, including gastrointestinal and pulmonary infections, respond less well to ganciclovir than does retinitis.

Ganciclovir is also valuable for prophylaxis and early treatment of CMV infections in *transplant recipients*.[7,15-22] It is not clear whether pre-emptive therapy in infected patients is a better strategy than prophylaxis.[23] For established infections, ganciclovir is reported to be more effective in solid organ transplant recipients than in bone marrow transplant recipients. Ganciclovir has also been tried for prevention of CMV infection in patients with AIDS, although results are conflicting.[24,25]

Treatment of *congenital infections* has a generally poor outcome. Prolonged treatment periods may improve the response, but the safety of extended treatment with ganciclovir in this age group has not been fully evaluated and there is a need for further randomised controlled studies.[26] There is some evidence[27,28] that a 6-week course started in neonates with clinically apparent disease affecting the CNS prevents hearing deterioration at 6 months and may also prevent deterioration at or beyond 1 year of age.

1. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. *N Engl J Med* 1992; 326: 213–20.
2. Polis MA, *et al.* Increased survival of a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis who received sodium phosphonoformate (foscarnet). *Am J Med* 1993; 94: 175–80.
3. D'Alessandro AM, *et al.* Successful treatment of severe cytomegalovirus infections with ganciclovir and CMV hyperimmune globulin in liver transplant recipients. *Transplant Proc* 1989; 21: 3560–1.
4. Salmela K, *et al.* Ganciclovir in the treatment of severe cytomegalovirus disease in liver transplant patients. *Transplant Proc* 1990; 22: 238–40.
5. Emanuel D, *et al.* Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; 109: 777–82.
6. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS: the Cytomegalovirus Retreatment Trial. *Arch Ophthalmol* 1996; 114: 23–33.
7. Mylonakis E, *et al.* Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. *Clin Infect Dis* 2002; 34: 1337–41.
8. Anand R, *et al.* Control of cytomegalovirus retinitis using sustained release of intraocular gancyclovir. *Arch Ophthalmol* 1993; 111: 223–7.
9. Martin DF, *et al.* Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol* 1994; 112: 1531–9.
10. Musch DC, *et al.* Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. *N Engl J Med* 1997; 337: 83–90.
11. Ausayakhun S, *et al.* Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. *J Med Assoc Thai* 2005; 88 (suppl 9): S15–520.
12. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; 131: 396–7.
13. Martin DF, *et al.* Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999; 340: 1063–70.
14. Lalezari JP, *et al.* High dose oral ganciclovir treatment for cytomegalovirus retinitis. *J Clin Virol* 2002; 24: 67–77.
15. Goodrich JM, *et al.* Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med* 1993; 118: 173–8.
16. Winston DJ, *et al.* Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. *Ann Intern Med* 1993; 118: 179–84.
17. Hibberd PL, *et al.* Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; 123: 18–26.
18. Winston DJ, *et al.* Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995; 346: 69–74.
19. Gane E, *et al.* Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. *Lancet* 1997; 350: 1729–33.
20. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. *Clin Infect Dis* 2001; 32: 742–51.
21. Paya CV, *et al.* Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002; 185: 854–60.
22. Keven K, *et al.* Cytomegalovirus prophylaxis using oral ganciclovir or valganciclovir in kidney and pancreas-kidney transplantation under antibody preconditioning. *Transplant Proc* 2004; 36: 3107–12.
23. Monforte V, *et al.* Preemptive therapy with intravenous ganciclovir for the prevention of cytomegalovirus disease in lung transplant recipients. *Transplant Proc* 2005; 37: 4039–42.
24. McCarthy M. Oral ganciclovir fails to prevent CMV in HIV trial. *Lancet* 1995; 346: 895.
25. Spector SA, *et al.* Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. *N Engl J Med* 1996; 334: 1491–7.
26. Michaels MG, *et al.* Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 2003; 22: 504–8.
27. Kimberlin DW, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; 143: 16–25.
28. Oliver SE, *et al.* National Institute of Allergy, Infectious Diseases Collaborative Antiviral Study Group. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009; 46 (suppl 4): S22–S26.

Epstein-Barr virus infections. There have been anecdotal reports[1-4] of some improvement in patients with Epstein-Barr virus (EBV) infection given ganciclovir, although no antiviral therapy is entirely satisfactory (p. 955.1).

1. Pirsch JD, *et al.* Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir: two cases after solid organ transplantation. *Am J Med* 1989; 86: 241–4.
2. Ishida Y, *et al.* Ganciclovir for chronic active Epstein-Barr virus infection. *Lancet* 1993; 341: 560–1.
3. MacGinley R, *et al.* Epstein-Barr virus encephalitis in a renal allograft recipient diagnosed by polymerase chain reaction on cerebrospinal fluid and successfully treated with ganciclovir. *Nephrol Dial Transplant* 2001; 16: 197–8.
4. Adams LA, *et al.* Ganciclovir and the treatment of Epstein-Barr virus hepatitis. *J Gastroenterol Hepatol* 2006; 21: 1758–60.

Herpesvirus infections. The treatment of acute herpetic epithelial keratitis with topical ganciclovir 0.15% gel has been reviewed.[1,2] Ganciclovir gel is licensed in many countries for the treatment of superficial ocular infections with herpes simplex (p. 955.2). Studies have suggested that it is as effective as 3% aciclovir ointment, and may perhaps be better tolerated.[1]

1. Colin J. Ganciclovir ophthalmic gel, 0.15%: a valuable tool for treating ocular herpes. *Clin Ophthalmol* 2007; 1: 441–53.
2. Tabbara KF, Al Balushi N. Topical ganciclovir in the treatment of acute herpetic keratitis. *Clin Ophthalmol* 2010; 4: 905–12.

Adverse Effects and Treatment

The most common adverse effects of systemic ganciclovir are haematological and include neutropenia and thrombocytopenia; anaemia also occurs. Neutropenia affects up to 50% of patients given ganciclovir, most commonly starting in the first or second week of use. It is usually reversible but may be prolonged or irreversible and can lead to potentially fatal infections. AIDS patients may be at a greater risk of neutropenia than other immunosuppressed patients. Thrombocytopenia occurs in about 20% of patients given ganciclovir. Those with iatrogenic immunosuppression may be more at risk of developing thrombocytopenia than AIDS patients. Other adverse effects occurring in patients given systemic ganciclovir include dyspnoea, headache, fever, rash, pruritus, asthenia, CNS and gastrointestinal disturbances, infection, increased serum-creatinine concentration, and abnormal liver function tests. Less frequent adverse effects reported include anaphylaxis, arrhythmias, hypotension, pancreatitis, haematuria, as well as metabolic, musculoskeletal, urogenital, and cutaneous symptoms. When given intravenously, irritation or phlebitis may occur at the site of injection due to the high pH.

Local adverse effects have been associated with the insertion of ocular implants of ganciclovir and use of the topical eye gel.

Animal studies have suggested that there may be a risk of adverse testicular effects with temporary or permanent inhibition of spermatogenesis. Female fertility may also be affected. Such studies also suggest that ganciclovir is a potential mutagen, teratogen, and carcinogen.

Haemodialysis and hydration may be useful in reducing plasma concentrations of ganciclovir. Haematological adverse effects may be reversed in some patients by stopping treatment or reducing dosage; blood cell counts should return to normal within 3 to 7 days.

Colony-stimulating factors have been given with ganciclovir to limit its haematological toxicity.

Effects on the blood. Ganciclovir-induced neutropenia was successfully treated in a patient with CMV retinitis and bone-marrow suppression by *molgramostim* 5 micrograms/kg daily by intravenous infusion.[1] In a multicentre, randomised placebo-controlled study[2] in 69 AIDS patients with CMV infection who developed neutropenia from ganciclovir therapy, *lenograstim* given in a daily dose of 50 micrograms/m^2 subcutaneously yielded similar positive results.

1. Russo CL, *et al.* Treatment of neutropenia associated with dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor. *Lancet* 1990; 336: 751–2.
2. Dubreuil-Lemaire, M-L. *et al.* Lenograstim for the treatment of neutropenia in patients receiving ganciclovir for cytomegalovirus infection: a randomised, placebo-controlled trial in AIDS patients. *Eur J Haematol* 2000; 65: 337–43.

Effects on mental function. Psychosis has been associated with intravenous ganciclovir use in 2 patients with normal renal function.[1,2] In both cases, psychotic symptoms such as agitation, confusion, and hallucination, occurred within 2 to 6 days of starting treatment with ganciclovir; symptoms resolved after ganciclovir was stopped.

1. Hansen BA, *et al.* Ganciclovir-induced psychosis. *N Engl J Med* 1996; 335: 1397.
2. Southworth MR, Dunlap SH. Psychotic symptoms and confusion associated with intravenous ganciclovir in a heart transplant recipient. *Pharmacotherapy* 2000; 20: 479–83.

Effects on the skin. An interstitial granulomatous drug reaction was reported[1] in a 57-year old woman after about one month of treatment with intravenous ganciclovir for CMV pneumonia. No other new drugs were given before

the onset of the lesions and they resolved spontaneously within 2 weeks of stopping the ganciclovir.

1. Marcollo Pini A, *et al.* Interstitial granulomatous drug reaction following intravenous ganciclovir. *Br J Dermatol* 2008; 158: 1391–3.

Precautions

Ganciclovir should be used with caution in patients with renal impairment and doses should be adjusted according to creatinine clearance. It should not be given by rapid or bolus injection and adequate hydration should be maintained during intravenous infusion. It should be given with caution to patients with low blood counts or with a history of cytopenic reactions to drugs. Complete blood and platelet counts should be performed every 2 days or daily during the first 14 days of intravenous therapy and once weekly thereafter; ganciclovir should be withdrawn if the neutrophil count falls below 500 cells/microlitre or the platelet count falls below 25 000 cells/microlitre. Patients receiving oral ganciclovir should also be monitored regularly.

Ganciclovir is contra-indicated in pregnancy; contraception is recommended during ganciclovir treatment and, additionally for men, for 90 days thereafter. Adverse effects have occurred in the offspring of *animals* given ganciclovir during pregnancy and lactation.

Because of the risk of carcinogenicity and the high pH of the solution, contact with the skin and eyes should be avoided during the reconstitution of ganciclovir sodium injection.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ganciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Sodium content. Each g of ganciclovir sodium contains about 3.6 mmol of sodium.

Interactions

Zidovudine given with ganciclovir may have an additive neutropenic effect and should not normally be given during intravenous ganciclovir induction therapy, although it has been given with caution during oral maintenance therapy. Probenecid and other drugs that inhibit renal tubular secretion and resorption may reduce the renal clearance of ganciclovir, and so increase its serum concentrations. Use of intravenous ganciclovir with oral mycophenolate mofetil may result in increased plasma concentrations of both drugs due to competition for renal tubular secretion. Drugs that inhibit rapid cell division such as amphotericin B, some antineoplastic drugs, co-trimoxazole, dapsone, flucytosine, hydroxycarbamide, nucleoside analogues, and pentamidine may have additive toxic effects if given with ganciclovir. Convulsions have been reported when ganciclovir was given with imipenem and cilastatin.

Antivirals. Additive haematological toxicity, including neutropenia, may occur if ganciclovir is given with *zidovudine* (see Zidovudine, p. 1026.3), and there are reports of increased plasma concentrations of *didanosine* when given with ganciclovir (see p. 974.1). There has also been a report[1] of decreased blood concentrations of ganciclovir when didanosine (200 mg every 12 hours) was given orally 2 hours before oral ganciclovir (1 g every 8 hours) but not when the two drugs were given at the same time. However, a later study[2] using twice the dose of oral ganciclovir found no effect irrespective of whether ganciclovir was given 2 hours before or 2 hours after didanosine.

When ganciclovir was given orally with *zalcitabine*, a 22% increase in the area under the concentration-time curve for ganciclovir was noted although it was believed that this did not necessitate any dosage modification.[3] No pharmacokinetic changes were reported when ganciclovir was given orally with *stavudine*.[3]

1. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 17: 227–34.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; 38: 1057–62.
3. Jung D, *et al.* The pharmacokinetics and safety profile of oral ganciclovir combined with zalcitabine or stavudine in asymptomatic HIV- and CMV-seropositive patients. *J Clin Pharmacol* 1999; 39: 505–12.

Ciclosporin. Reversible acute unilateral or bilateral eye movement disorders typical of sixth cranial nerve palsies[1] occurred in 4 patients who received ciclosporin and ganciclovir after bone marrow transplantation.

1. Openshaw H, *et al.* Eye movement disorders in bone marrow transplant patients on cyclosporin and ganciclovir. *Bone Marrow Transpl* 1997; 19: 503–5.

Antiviral Action

Ganciclovir inhibits replication of human herpesviruses *in vivo* and *in vitro*. It is active against CMV, herpes simplex virus types 1 and 2, Epstein-Barr virus, varicella-zoster virus, herpesvirus 6, 7, and 8, and hepatitis B virus. This activity is due to intracellular conversion of ganciclovir by viral thymidine kinase (in herpes simplex and varicella-zoster infected cells) or possibly by cellular deoxyguanosine kinase (in Epstein-Barr infected cells) to ganciclovir monophosphate with subsequent cellular conversion to the diphosphate and the active triphosphate. Ganciclovir triphosphate inhibits viral DNA synthesis by inhibiting the viral DNA polymerase enzyme as well as being incorporated into the viral DNA. This process is selective for infected cells; the concentration of ganciclovir triphosphate may be up to a hundredfold higher in CMV-infected cells than in uninfected cells.

Ganciclovir has a similar spectrum of activity to aciclovir, herpes simplex virus types 1 and 2 being the most susceptible of the herpesviruses. However, CMV is much more susceptible to ganciclovir than aciclovir.

Resistance to ganciclovir has been found *in vitro* in herpes simplex viruses, varicella-zoster virus, and CMV. Possible mechanisms of resistance include a reduction in the phosphorylation of ganciclovir to the active form and reduced sensitivity of viral DNA polymerase. Resistance has been reported in CMV strains isolated from patients receiving ganciclovir for prolonged periods and in those with an initially high viral load. It has also been seen in AIDS patients with CMV retinitis who have never previously received the drug. Ganciclovir-resistant strains of CMV are cross-resistant to aciclovir (even at the highest doses); cross-resistance with cidofovir and foscarnet have been described, however, other studies have found ganciclovir-resistant strains remain susceptible to cidofovir, foscarnet, and vidarabine.

Resistance. The development of CMV resistance to ganciclovir may be a factor in disease progression in patients receiving prolonged therapy with ganciclovir and the incidence of resistance is reported to increase with duration of therapy.[1] A ganciclovir-resistant isolate of CMV was detected in about 30% of 95 patients after 9 months of treatment and this correlated with dissemination of infection to the contralateral eye.[2] Treatment of unilateral retinitis with systemic ganciclovir (intravenously, or orally together with an implant) was associated with a higher incidence of ganciclovir-resistant CMV infection developing in the contralateral eye, compared with treatment with ganciclovir implant alone.[3]

Ganciclovir-resistant CMV has been reported[4] to be an important cause of late morbidity in seronegative patients who received CMV-seropositive organ transplants; in one study,[5] 5 of 67 seronegative recipients developed ganciclovir-resistant CMV disease compared with none of 173 seropositive subjects. The management of ganciclovir-resistant CMV has been reviewed.[6]

1. Drew WL. Cytomegalovirus resistance to antiviral therapies. *Am J Health-Syst Pharm* 1996; 53 (suppl 2): S17–S23.
2. Jabs DA, *et al.* Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. *J Infect Dis* 1998; 177: 770–3.
3. Imai Y, *et al.* Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. *J Infect Dis* 2004; 189: 611–15.
4. Limaye AP. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. *Clin Infect Dis* 2002; 35: 866–72.
5. Limaye AP, *et al.* Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; 356: 645–9.
6. Avery RK. Update in management of ganciclovir-resistant cytomegalovirus infection. *Curr Opin Infect Dis* 2008; 21: 433–7.

Resistance

Resistance to ganciclovir has been found *in vitro* in herpes simplex viruses, varicella-zoster virus, and CMV. Possible mechanisms of resistance include a reduction in the phosphorylation of ganciclovir to the active form and reduced sensitivity of viral DNA polymerase. Resistance has been reported in CMV strains isolated from patients receiving ganciclovir for prolonged periods and in those with an initially high viral load. It has also been seen in AIDS patients with CMV retinitis who have never previously received the drug. Cross-resistance with cidofovir is common.

Pharmacokinetics

Ganciclovir is poorly absorbed from the gastrointestinal tract after oral doses and there is minimal systemic absorption after intravitreal injection. Bioavailability of oral ganciclovir is about 5%, and is increased by intake with food to 6 to 9%. After intravenous dosage as ganciclovir sodium it is widely distributed to body tissues and fluids including intra-ocular fluid and CSF. Binding to plasma proteins is reported to be 1 to 2%. Ganciclovir is excreted unchanged in the urine mainly by glomerular filtration and also active tubular secretion. In patients with normal renal function the half-life is about 2.5 to 4.5 hours after intravenous doses and about 4 to 5.7 hours after oral doses. In patients with renal impairment, the renal clearance decreases and the half-life increases; a half-life of 28.5 hours has been reported when the serum-creatinine concentration was greater than 398 micromol/litre.

Haemodialysis has been reported to reduce plasma-ganciclovir concentrations by about 50%.

References.

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6. Jung D, *et al.* Steady-state relative bioavailability of three oral ganciclovir dosage regimens delivering 6,000 mg/day in patients with human immunodeficiency virus. *J Clin Pharmacol* 1998; 38: 1021–4.
7. Jung D, *et al.* Absolute bioavailability and dose proportionality of oral ganciclovir after ascending multiple doses in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; 38: 1122–8.
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14. Welker H, *et al.* Ganciclovir pharmacokinetic parameters do not change when extending valganciclovir cytomegalovirus prophylaxis from 100 to 200 days. *Transplantation* 2010; 90: 1414–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ciganclor; Cymevene; Gasmilen; Grinevel; Neagel; Virgan; ***Austral.***: Cymevene; Vitrasert; Vitrisert; ***Austria***: Cymevene; ***Belg.***: Cymevene; Virgan; ***Braz.***: Cymevene; Ganciclotrat; Ganvirax; ***Canad.***: Cytovene; ***Chile***: Cymevene; ***China***: Ai Lin Wei (艾林维); Ao Xi Tong (奥西彤); Bo Ying (博应); Cheng Li Kang (诚力康); Cymevene (赛美维); Di Du (迪都); Du Ya Xin (独雅欣); Fu Er Ling (孚尔灵); Gen Le Wei (更乐韦); He Pu Xin (荷普欣); He Yuan (贺元); Heng Kang (恒抗); Hong Kang Wei; Hui Teng (辉腾); Ji Xi Tong (集希通); Jun Fen (君芬); Kai Ji Wei (凯济维); Le Fan (了凡); Li Bai Lu (利百路); Li Jian (利健); Li Ke Le (丽科乐); Li Ke Ming (丽科明); Li Ke Qing (丽科清); Li Ke Wei (丽科伟); Lin Ke Hong (林可宏); Luoheng (罗恒); Mei Li Neng (美立能); Mei Si Bo Wei (美斯博维); Mei Ti Bo Wei (美替博伟); Ning Dan Xin (宁丹欣); Nuo Bei Qi (诺贝奇); Nuo Hao (诺好); Nuowei (诺伟); Pu Gen Xin (普更欣); Rui Sheng Yi (瑞圣亿); Shi De (实得); Si Ze (思泽); Wei Ke Rui Da (威克锐达); Wei Ru (维如); Weisi (韦斯); Xi Wei (希韦); Xin Qing Yu (新青羽); You Ni Da (尤尼达); Zhong Jia Tai (中佳太); ***Cz.***: Cymevene; Virgan; ***Denm.***: Cymevene; ***Fin.***: Cymevene; ***Fr.***: Cymevan; Virgan; ***Ger.***: Cymeven; Virgan; ***Gr.***: Cymevene; Virgan; ***Hong Kong***: Cymevene; Virgan†; ***Hung.***: Cymevene; Virgan; ***India***: Cymevene; Ganguard; Gavir; Natdovir; ***Indon.***: Cymevene; ***Irl.***: Cymevene; ***Israel***: Cymevene; ***Ital.***: Citovirax; Cymevene; Virgan; ***Malaysia***: Cymevene; ***Mex.***: Cymevene†; Umecorril; ***Neth.***: Cymevene; ***Norw.***: Cymevene; ***NZ***: Cymevene; ***Philipp.***: Cymevene; Virgan; ***Pol.***: Cymevene; Virgan; ***Port.***: Cymevene; Virgan; ***Rus.***: Cymevene (Цимевен); ***S.Afr.***: Cymevene; ***Singapore***: Cymevene; ***Spain***: Cymevene; Virgan; ***Swed.***: Cymevene; ***Switz.***: Cymevene; ***Thai.***: Cymevene; ***Turk.***: Cymevene; ***UK***: Cymevene; Virgan; ***Ukr.***: Cymevene (Цимевен); ***USA***: Cytovene; Vitrasert†; Zirgan; ***Venez.***: Cymevene.

Pharmacopoeial Preparations

USP 36: Ganciclovir for Injection; Ganciclovir Oral Suspension.

Ibacitabine *(rINN)*

Ibacitabin; Ibacitabina; Ibacitabinum; Iododesoxycytidine; Ибацитабин.

2′-Deoxy-5-iodocytidine.

$C_9H_{12}IN_3O_4$=353.1

CAS — 611-53-0.

ATC — D06BB08.

ATC Vet — QD06BB08.

UNII — 3EK8532DZV.

Profile

Ibacitabine is an antiviral used topically as a 1% gel in the treatment of herpes labialis (see Herpes Simplex Infections, p. 955.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Cuterpes; *Gr.*: Marenil.

Idoxuridine *(BAN, USAN, rINN)*

Allergan 211; GF-115; Idoksuridiini; Idoksuridinas; Idoxuridin; Idoxuridina; Idoxuridinum; IDU; 5-IDUR; 5-IUDR; NSC-39661; SKF-14287; Идоксуридин.

2′-Deoxy-5-iodouridine.

$C_9H_{11}IN_2O_5$=354.1

CAS — 54-42-2.

ATC — D06BB01; J05AB02; S01AD01.

ATC Vet — QD06BB01; QJ05AB02; QS01AD01.

UNII — LGP81V5245.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Idoxuridine). A white or almost white crystalline powder. M.p. about 180 degrees, with decomposition. Slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 36: (Idoxuridine). A white, practically odourless, crystalline powder. Slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Iodine vapour is liberated on heating idoxuridine. It has been reported that some decomposition products such as iodouracil are more toxic than idoxuridine and reduce its antiviral activity.

Uses and Administration

Idoxuridine is a pyrimidine nucleoside structurally related to thymidine. It is used topically in the treatment of herpes simplex keratitis and cutaneous infections with herpes simplex (p. 955.2) and herpes zoster (see Varicella-zoster Infections, p. 956.2), but has generally been superseded by other antivirals.

In the treatment of herpes simplex keratitis, idoxuridine is applied as a 0.1% ophthalmic solution and has also been used as a 0.5% eye ointment.

Idoxuridine 5% in dimethyl sulfoxide (to aid absorption) may be painted onto the lesions of cutaneous herpes simplex and herpes zoster four times daily for 4 days.

Adverse Effects

Hypersensitivity reactions such as irritation, pain, and pruritus may occur occasionally when idoxuridine is applied to the eyes. Other adverse effects include stinging, conjunctivitis, oedema and inflammation of the eye or eyelids, photophobia, pruritus, and rarely, occlusion of the lachrymal duct. Prolonged or excessive use may damage the cornea.

Idoxuridine applied to the skin may produce irritation, stinging, and hypersensitivity reactions. Taste disturbance may also occur. Excessive application of topical idoxuridine to the skin may cause skin maceration.

Idoxuridine is a potential carcinogen and teratogen.

Carcinogenicity. Squamous cell carcinoma developed in a young woman after topical applications of idoxuridine for 4 days for the treatment of herpes simplex labialis.[1]

1. Koppang HS, Aas E. Squamous carcinoma induced by topical idoxuridine therapy? *Br J Dermatol* 1983; 108: 501–3.

Precautions

Idoxuridine should be used with caution in conditions where there is deep ulceration involving the stromal layers of the cornea, as delayed healing has resulted in corneal perforation. Prolonged topical use should be avoided.

The potential teratogenicity of idoxuridine should be taken into account when treating pregnant patients or patients likely to become pregnant. Corticosteroids should be applied with caution in patients also receiving idoxuridine as they may accelerate the spread of viral infection.

Interactions

Preparations containing boric acid should not be applied to the eye in patients also receiving ocular preparations of idoxuridine as irritation ensues.

Antiviral Action

After intracellular phosphorylation to the triphosphate, idoxuridine is incorporated into viral DNA instead of thymidine so inhibiting replication of sensitive viral strains. Idoxuridine is also incorporated into mammalian DNA. Idoxuridine is active against herpes simplex and varicella zoster viruses. It has also been shown to inhibit vaccinia virus, CMV, and adenovirus.

Pharmacokinetics

Penetration of idoxuridine into the cornea and skin is reported to be poor. Idoxuridine is rapidly metabolised in the body to iodouracil, uracil, and iodide, which are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Idulea; *Austral.*: Stoxil†; *Braz.*: Herpesine; *Canad.*: Herplex†; *Ger.*: Virunguent†; *India*: Idurin; Ridinox†; *Indon.*: Isotic Ixodine†; *Ital.*: Iducher; Idustatin; *Neth.*: Virexen†; *NZ*: Virasolve; *Rus.*: Oftan IDU (Офтан ИДУ); *Singapore*: Virunguent; *Spain*: Virexen; *Switz.*: Virunguent†; *UK*: Herpid†.

Multi-ingredient Preparations. *Austral.*: Virasolve.

Pharmacopoeial Preparations

BP 2014: Idoxuridine Eye Drops;

USP 36: Idoxuridine Ophthalmic Ointment; Idoxuridine Ophthalmic Solution.

Imiquimod *(BAN, USAN, rINN)*

Imikimod; Imikimodi; Imiquimodum; R-837; S-26308; Имихимод.

4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline.

$C_{14}H_{16}N_4$=240.3

CAS — 99011-02-6.

ATC — D06BB10.

ATC Vet — QD06BB10.

UNII — P1QW714R7M.

Uses and Administration

Imiquimod is an immune response modifier used topically in the treatment of external genital and perianal warts (p. 1689.3), superficial basal cell carcinomas, and actinic keratoses (see Malignant Neoplasms of the Skin, below). For the treatment of genital and perianal warts, it is applied as a 5% cream three times each week for up to 16 weeks and is left on the skin for 6 to 10 hours. For the management of superficial **basal cell carcinoma**, a 5% cream is applied 5 times each week for 6 weeks and left on the skin for about 8 hours. For the treatment of **actinic keratoses** on the face or scalp, a 5% cream is also used and is again left on the skin for 8 hours. In the UK, this is applied 3 times each week for 4 weeks, repeated after a 4-week break for a further 4 weeks if necessary; in the USA, application twice a week for 16 weeks is recommended.

Imiquimod is also under investigation for the treatment of other squamous cell carcinomas.

References

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5. Harwood CA, *et al.* Imiquimod cream 5% for recalcitrant cutaneous warts in immunosuppressed individuals. *Br J Dermatol* 2005; 152: 122–9.
6. Ulrich C, *et al.* Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. *Br J Dermatol* 2007; 157 (suppl 2): 25–31.
7. Stockfleth E, *et al.* Multicentre, open-label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head. *Br J Dermatol* 2007; 157 (suppl 2): 41–6.
8. Schöfer H. Evaluation of imiquimod for the therapy of external genital and anal warts in comparison with destructive therapies. *Br J Dermatol* 2007; 157 (suppl 2): 52–5.
9. Ganjian S, *et al.* Off-label indications for imiquimod. *Dermatol Online J* 2009; 15: 4.
10. Trakatelli M, *et al.* Efforts to counteract locally the effects of systemic immunosupression: a review on the use of imiquimod, a topical immunostimulator in organ transplant recipients. *Int J Immunopathol Pharmacol* 2010; 23: 387–96.

Leishmaniasis. Evidence from small studies[1,2] suggests that topical imiquimod 5 or 7.5% cream with parenteral meglumine antimonate (p. 926.3) may be of use in the management of cutaneous leishmaniasis (p. 922.1).

For mention of the use of imiquimod with dapsone in itraconazole for treatment of cutaneous leishmaniasis, see under Dapsone, p. 281.3 and Itraconazole, p. 584.2, respectively.

1. Miranda-Verástegui C, *et al.* Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. *Clin Infect Dis* 2005; 40: 1395–1403.
2. Arevalo I, *et al.* Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clin Infect Dis* 2007; 44: 1549–54.

Malignant neoplasms of the skin. Imiquimod is indicated in the treatment of actinic keratosis[1–4] and basal cell carcinoma (p. 714.2).[5–9] It has also been reported to be effective in the treatment of cutaneous T-cell lymphomas such as mycosis fungoides (p. 698.3)[10–12] and in a patient with CD30+ anaplastic large cell lymphoma.[12] Two patients with cutaneous B-cell lymphoma had a partial remission after treatment with topical imiquimod, while one did not respond to therapy;[12] however, a patient with primary cutaneous follicle centre lymphoma was successfully treated.[13] Imiquimod is under investigation for the treatment of Bowen's disease.[14] It has also been tried in lentigo maligna[15] and other forms of localised or *in-situ* melanoma,[16,17] and there are also reports of investigational use in the management of metastatic melanoma.[18,19] and in anal and vulvar intraepithelial neoplasia.[20–22]

1. Lebwohl M, *et al.* Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004; 50: 714–21.
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3. Krawtchenko N, *et al.* A randomised study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol* 2007; 157 (suppl 2): 34–40.
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8. Bath-Hextall FJ, *et al.* Interventions for basal cell carcinoma of the skin. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
9. Love WE, *et al.* Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol* 2009; 145: 1431–8.
10. Deeths MJ, *et al.* Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. *J Am Acad Dermatol* 2005; 52: 275–80.
11. Martínez-González MC, *et al.* Imiquimod in mycosis fungoides. *Eur J Dermatol* 2008; 18: 148–52.
12. Coors EA, *et al.* Topical imiquimod as treatment for different kinds of cutaneous lymphoma. *Eur J Dermatol* 2006; 16: 391–3.
13. Stavrakoglou A, *et al.* Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. *Br J Dermatol* 2007; 157: 620–2.
14. Mackenzie-Wood A, *et al.* Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol* 2001; 44: 462–70.
15. Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; 155: 653–6.
16. Lonsdale-Eccles AA, *et al.* Successful treatment of vulval melanoma in situ with topical 5% imiquimod cream. *Br J Dermatol* 2006; 155: 215–17.
17. Spieth K, *et al.* Topical imiquimod: effectiveness in intraepithelial melanoma of oral mucosa. *Lancet Oncol* 2006; 7: 1036–7.
18. Zeitouni NC, *et al.* Treatment of cutaneous metastatic melanoma with imiquimod 5% cream and the pulsed-dye laser. *Br J Dermatol* 2005; 152: 376–7.
19. Utikal J, *et al.* Complete remission of multiple satellite and in-transit melanoma metastases after sequential treatment with isolated limb perfusion and topical imiquimod. *Br J Dermatol* 2006; 155: 488–91.
20. Wieland U, *et al.* Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006; 142: 1438–44.
21. van Seters M, *et al.* Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008; 358: 1465–73.
22. Mahto M, *et al.* More than a decade on: review of the use of imiquimod in lower anogenital intraepithelial neoplasia. *Int J STD AIDS* 2010; 21: 8–16.

Skin disorders. Applications of imiquimod 5% have shown some benefit in a few patients with localised scleroderma (morphoea).[1] It has also been successfully used to treat lesions of human papillomavirus type 5 in a patient with familial benign pemphigus (Hailey-Hailey disease)[2]; intra-oral applications were used in patients with human papillomavirus-associated oral leucoplakia to reduce the area of leucoplakia and thereby facilitate surgical removal of the residual lesions if necessary.[3]

Topical imiquimod appears to have antiangiogenic properties and has been tried for treatment of some infants with infantile haemangiomas[4–6] and a patient with capillary malformations;[7] treatment was beneficial in most patients.

1. Dytoc M, *et al.* First case series on the use of imiquimod for morphoea. *Br J Dermatol* 2005; 153: 815–20.
2. Chan CC, *et al.* Human papillomavirus type 5 infection in a patient with Hailey-Hailey disease successfully treated with imiquimod. *Br J Dermatol* 2007; 156: 579–81.
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5. Ho NT, *et al.* Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. *J Am Acad Dermatol* 2007; 56: 63–8.
6. Martinez ML *et al.* Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol* 2002; 138: 881–4.
7. Kouba DJ, *et al.* Topical imiquimod in the treatment of a long-standing capillary malformation. *Br J Dermatol* 2007; 157: 1071–2.

Adverse Effects and Precautions

Adverse effects after topical application of imiquimod include local skin erosion, erythema, excoriation, flaking, and oedema. There have been reports of localised hypopigmentation and hyperpigmentation. Skin reactions away from the site of application have been reported. Systemic effects after topical application include headache, flu-like symptoms, and myalgia. Hepato-biliary disorders, including severe cases, have been reported rarely after topical imiquimod use.

Hypotension has occurred after repeated ingestion.

Hypersensitivity. Angioedema, initially of both the hands and feet and later the tongue, occurred in a 61-year-old man 3 weeks after starting treatment with a 5% imiquimod cream for squamous cell carcinoma *in situ* (Bowen's disease).[1]

1. Barton JC. Angioedema associated with imiquimod. *J Am Acad Dermatol* 2004; 51: 477–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imiquimod as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aldara; Imimore; Miquimod; Quinilan; Virosupril; *Austral.*: Aldara; *Austria*: Aldara; *Belg.*: Aldara; *Braz.*: Aldara; Imoxy; Ixium; Modik; *Canad.*: Aldara; Vyloma; Zyclara; *Chile*: Aldara†; Imimor; Labimiq; Tocasol; *China*: Aldara (艾达乐); Li Di (利迪); Li Ke Jie (丽科杰); Nan Bo (南博); Tian Rui (天锐); Youbiqing (优必青); *Cz.*: Aldara; *Denm.*: Aldara; *Fin.*: Aldara; *Fr.*: Aldara; *Ger.*: Aldara; *Gr.*: Aldara; *Hong Kong*: Aldara; *Hung.*: Aldara; *India*: Imiquad; Nilwart; *Irl.*: Aldara; *Israel*: Aldara; Aquimod; *Ital.*: Aldara; *Jpn*: Beselna; *Malaysia*: Aldara; *Mex.*: Aldara; Vetland; *Neth.*: Aldara; *Norw.*: Aldara; *NZ*: Aldara; *Philipp.*: Aldara; *Pol.*: Aldara; *Port.*: Aldara; *S.Afr.*: Aldara; *Singapore*: Aldara; *Spain*: Aldara; *Swed.*: Aldara; *Switz.*: Aldara; *Thai.*: Aldara; *Turk.*: Aldara; *UK*: Aldara; Zyclara; *Ukr.*: Aldara (Алдара); *USA*: Aldara; Zyclara.

Indinavir Sulfate *(BANM, USAN, pINNM)*

Indinavir, sulfate d'; Indinavir, sulfato de; Indinavir Sulphate; Indinavir sulfas; Indinavirsulfat; L-735524; MK-0639; MK-639; Sulfato de indinavir; Индинавира Сульфат.

(αR,γS,2S)-α-Benzyl-2-(*tert*-butylcarbamoyl)-γ-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinepentanamide sulfate (1:1).

$C_{36}H_{47}N_5O_4,H_2SO_4$=711.9

CAS — 150378-17-9 (indinavir); 157810-81-6 (indinavir sulfate).

ATC — J05AE02.

ATC Vet — QJ05AE02.

UNII — 771H53976Q.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Indinavir Sulfate). A white or almost white, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 36: (Indinavir Sulfate). A white or almost white, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from moisture.

Uses and Administration

Indinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when indinavir is used alone, and it is therefore used with other antiretrovirals.

Indinavir is given orally as the sulfate, but doses are expressed in terms of the base; 116 mg of indinavir sulfate is equivalent to about 100 mg of indinavir. It is given in a usual adult dose of 800 mg every 8 hours. Doses of indinavir may need to be adjusted to manage significant drug interactions. If used with delavirdine, a *reduced* indinavir dose of 400 to 600 mg every 8 hours should be considered. Similarly, a dose of 600 mg every 8 hours is recommended when indinavir is used with itraconazole or ketoconazole; restriction of the azole doses should also be considered (see Uses and Administration of Itraconazole, p. 583.3, and Ketoconazole, p. 585.3, respectively). If given with rifabutin, indinavir doses should be *increased* to 1 g every 8 hours (the dose of rifabutin must also be adjusted, see under Uses and Administration of Rifabutin, p. 349.1). Indinavir should be given either 1 hour before or 2 hours after meals, or with a light, low-fat meal. Adequate hydration should be maintained. Treatment may have to be interrupted if acute episodes of nephrolithiasis occur.

For details of doses in children and adolescents, see below. For details of modified dosage to be used in patients with hepatic impairment, see below.

References.
1. Rayner CR, *et al.* A critical evaluation of the therapeutic range of indinavir. *Ann Pharmacother* 2002; 36: 1230–7.
2. Boyd M. Indinavir: the forgotten HIV-protease inhibitor: does it still have a role? *Expert Opin Pharmacother* 2007; 8: 957–64.
3. Cressey TR, *et al.* Indinavir/ritonavir remains an important component of HAART for the treatment of HIV/AIDS, particularly in resource-limited settings. *Expert Opin Drug Metab Toxicol* 2007; 3: 347–61.

Administration in children. For the treatment of HIV infection in children 4 years of age and older indinavir is given orally with other antiretroviral drugs. A dose of 500 mg/m^2 every 8 hours is recommended; doses should not exceed the adult dose (see above).

Administration in hepatic impairment. A reduction in the oral dose of indinavir to 600 mg every 8 hours is recommended for patients with mild to moderate hepatic insufficiency due to cirrhosis.

Adverse Effects

The most commonly reported adverse effects associated with antiretroviral regimens containing indinavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea and vomiting), taste disturbances, headache, and dizziness. Nephrolithiasis, often with flank pain and occurring with or without haematuria, is the most frequently reported serious adverse effect. It appears to be dose-related and is more frequent in patients taking more than 2.4 g daily; it also occurs more often in children. Temporarily stopping treatment and giving fluids often resolve the symptoms, but interstitial nephritis and acute renal failure have been reported. Dry skin and rashes occur commonly and may occasionally be severe. Cases of Stevens-Johnson syndrome and erythema multiforme have also been reported. Hypersensitivity reactions, including vasculitis and sometimes anaphylaxis, have been associated with indinavir. Hepatitis, including cases resulting in hepatic failure and death has occurred. Cases of acute haemolytic anaemia have been reported again with some fatalities. Other commonly reported adverse effects are dry mouth, dysuria, fatigue, flatulence, hypoaesthesia, insomnia, paraesthesia, pruritus, and acid regurgitation. Neutrophil counts may be reduced and mean corpuscular volume increased. Abnormal laboratory test results associated with indinavir-containing regimens have included crystalluria, haematuria, proteinuria, raised liver enzymes, and asymptomatic hyperbilirubinaemia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including indinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including indinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Reviews.
1. Moyle GJ, Gazzard BG. A risk-benefit assessment of HIV protease inhibitors. *Drug Safety* 1999; 20: 299–321.

Effects on carbohydrate and lipid metabolism. HIV-protease inhibitors have been associated with a lipodystrophy syndrome characterised by peripheral fat wasting, central adiposity and the so called 'buffalo hump', hyperlipidaemia, and insulin resistance.[1]

A survey of 113 HIV-infected patients receiving HIV-protease inhibitors found lipodystrophy in 83% (severe in 11%) and impaired glucose tolerance in 23% (including diabetes mellitus in 7%) after a mean of 21 months of therapy.[2]

A systematic review[3] of published material has concluded that use of HIV-protease inhibitors is associated with increased concentrations of total cholesterol, triglycerides, and low-density lipoprotein; that use is often associated with morphological signs of cardiovascular disease such as increased carotid intima thickness or atherosclerotic lesions. Comparison of the effect of specific HIV-protease inhibitors showed that ritonavir was consistently associated with elevated lipids and that, although some studies showed that saquinavir was associated with elevated lipids, it was to a lesser degree than other drugs. Guidelines[4] have been published outlining the management, including drug therapy, of antiretroviral-induced lipid disorders in HIV-infected patients.

Impaired glucose tolerance has been linked to reduction in insulin sensitivity[5] and has responded to treatment with sulfonylureas or insulin.[6] Insulin resistance has been reported with some HIV-protease inhibitors (such as indinavir and ritonavir-boosted lopinavir), but not all; atazanavir has not been found to alter insulin sensitivity, regardless of whether it is ritonavir-boosted or not.[7]

1. Carr A, *et al.* Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351: 1881–3.
2. Carr A, *et al.* Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353: 2093–9.
3. Rhew DC, *et al.* Association between protease inhibitor use and increased cardiovascular risk in patients infected with human immunodeficiency virus: a systematic review. *Clin Infect Dis* 2003; 37: 959–72.
4. Dubé MP, *et al.* Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; 37: 613–27. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/378131 (accessed 28/08/08)
5. Walli R, *et al.* Impaired glucose tolerance and protease inhibitors. *Ann Intern Med* 1998; 129: 837–8.
6. Dubé MP, *et al.* Protease inhibitor-associated hyperglycaemia. *Lancet* 1997; 350: 713–14.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)

Effects on the cardiovascular system. Use of HIV-protease inhibitors has been associated with myocardial infarction and stroke in some cohort studies; risk appears to be greatest among patients with other risk factors for cardiovascular disease.[1] In a nested case-control study,[2] the risk of myocardial infarction was increased by cumulative exposure to all studied HIV-protease inhibitors except saquinavir, and particularly to ritonavir-boosted lopinavir and boosted or unboosted amprenavir/fosamprenavir.

For adverse effects of HIV-protease inhibitors on carbohydrate and lipid metabolism that increase the risk of coronary vascular disease, see above.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)
2. Lang S, *et al.* Clinical Epidemiology Group of the French Hospital Database on HIV. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med* 2010; 170: 1228–38.

Effects on the kidneys. Nephrolithiasis has been reported in about 10% of patients receiving indinavir, and the incidence may be higher in patients with haemophilia or hepatitis C infection.[1] In some cases, indinavir-induced nephrolithiasis may occur years after stopping the drug.[2] There have also been reports of nephrolithiasis in patients given atazanavir or fosamprenavir. Both asymptomatic[3] and symptomatic[4,5] crystalluria have been reported in patients receiving indinavir, with symptomatic urinary-tract disease in 8%. Indinavir has been identified as the major constituent of both urinary crystals[3] and calculi.[6] In addition there have been reports of acute interstitial nephritis associated with indinavir[7] and deterioration of renal function associated with both indinavir[8] and ritonavir.[9,10] Renal atrophy was associated with long-term treatment with indinavir.[11,12]

Factors that may increase the risk of indinavir crystallisation in the urine include volume depletion, hepatic insufficiency, low urinary pH, renal insufficiency or tubular cell injury, and low lean body-mass.[2]

1. Brodie SB, *et al.* Variation in incidence of indinavir-associated nephrolithiasis among HIV-positive patients. *AIDS* 1998; 12: 2433–7.
2. Huynh J, *et al.* Indinavir-induced nephrolithiasis three and one-half years after cessation of indinavir therapy. *Int Urol Nephrol* 2010. Available at: http://www.springerlink.com/content/54x727175v5j2362/fulltext.pdf (accessed 08/02/11)
3. Kopp JB, *et al.* Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997; 127: 119–25.

4. Hachey DM, *et al.* Indinavir crystalluria in an HIV-positive man. *Ann Pharmacother* 2000; 34: 403.
5. Famularo G, *et al.* Symptomatic crystalluria associated with indinavir. *Ann Pharmacother* 2000; 34: 1414–18.
6. Daudon M, *et al.* Urinary stones in HIV-1-positive patients treated with indinavir. *Lancet* 1997; 349: 1294–5.
7. Marroni M, *et al.* Acute interstitial nephritis secondary to the administration of indinavir. *Ann Pharmacother* 1998; 32: 843–4.
8. Boubaker K, *et al.* Changes in renal function associated with indinavir. *AIDS* 1998; 12: F249–F254.
9. Duong M, *et al.* Renal failure after treatment with ritonavir. *Lancet* 1996; 348: 693–4.
10. Chugh S, *et al.* Ritonavir and renal failure. *N Engl J Med* 1997; 336: 138.
11. Hanabusa H, *et al.* Renal atrophy associated with long-term treatment with indinavir. *N Engl J Med* 1999; 340: 392–3.
12. Cattelan AM, *et al.* Severe hypertension and renal atrophy associated with indinavir. *Clin Infect Dis* 2000; 30: 619–21.

Effects on the menstrual cycle. Irregular, prolonged, or heavy menstruation[1] in 4 patients receiving ritonavir subsequently returned to normal in the 3 who were transferred to a different HIV-protease inhibitor.

1. Nielsen H. Hypermenorrhoea associated with ritonavir. *Lancet* 1999; 353: 811–12.

Effects on mental state. Acute paranoid reactions occurred on two occasions in a patient receiving saquinavir.[1]

1. Finlayson JA, Laing RBS. Acute paranoid reaction to saquinavir. *Am J Health-Syst Pharm* 1998; 55: 2016–17.

Effects on the pancreas. Pancreatitis was associated with use of ritonavir with saquinavir in 1 patient,[1] and with ritonavir (other drugs unspecified) in 2 others,[2] and was believed to be secondary to hyperlipidaemia (see Effects on Carbohydrate and Lipid Metabolism, p. 986.2).

1. McBride M, *et al.* Lipid lowering therapy in patients with HIV infection. *Lancet* 1998; 352: 1782–3.
2. Di Perri G, *et al.* HIV-protease inhibitors. *N Engl J Med* 1998; 339: 773–4.

Effects on sexual function. Sexual dysfunction has been reported in patients given combination therapy with HIV-protease inhibitors and reverse transcriptase inhibitors.[1,2]

1. Martínez E, *et al.* Sexual dysfunction with protease inhibitors. *Lancet* 1999; 353: 810–11.
2. Colebunders R, *et al.* Sexual dysfunction with protease inhibitors. *Lancet* 1999; 353: 1802.

Effects on the skin. Rashes have been reported in about 20% of patients receiving indinavir and in 3 to 5% of patients receiving nelfinavir or saquinavir. Rash is described as a frequent adverse effect of ritonavir. In patients taking indinavir who reported rashes,[1] the rash commonly appeared within 2 weeks of starting treatment, was frequently accompanied by pruritus, and was usually self-limiting, commonly resolving within 4 weeks. Similar patterns have been reported with amprenavir/fosamprenavir (see p. 980.3).

Paronychia and pyogenic granuloma of the great toes has been reported in patients receiving indinavir.[2]

1. Gajewski LK, *et al.* Characterization of rash with indinavir in a national patient cohort. *Ann Pharmacother* 1999; 33: 17–21.
2. Bouscarat F, *et al.* Paronychia and pyogenic granuloma of the great toes in patients treated with indinavir. *N Engl J Med* 1998; 338: 1776–7.

Precautions

Indinavir is mainly metabolised in the liver and therefore caution and possible dosage reduction are required in hepatic impairment. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Although renal excretion is a relatively minor route of elimination, adequate hydration is recommended to reduce the risk of nephrolithiasis; monitoring is advised in the presence of renal impairment. Treatment may need to be temporarily interrupted or stopped completely in patients developing nephrolithiasis. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies indinavir as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. A retrospective survey[1] involving 89 women who received HIV-protease inhibitors during pregnancy indicated that these antivirals appeared generally safe. In the USA, guidelines[2] for the use of antiretroviral drugs in pregnant HIV-infected women suggest that when an HIV-protease inhibitor is required as part of an antiretroviral drug regimen for either maternal health or prevention of neonatal HIV transmission (see p. 959.1), ritonavir-boosted lopinavir is a drug of choice; suitable alternative HIV-protease inhibitors include nelfinavir, or ritonavir-boosted atazanavir, indinavir, or saquinavir.

1. Morris AB, *et al.* Multicenter review of protease inhibitors in 89 pregnancies. *J Acquir Immune Defic Syndr* 2000; 25: 306–11.
2. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Indinavir is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. It may compete for the same metabolic pathways with many drugs that are metabolised similarly, often resulting in mutually increased plasma concentrations. A drug that is a significant inducer of microsomal enzymes, particularly CYP3A4, may reduce plasma concentrations of indinavir. HIV-protease inhibitors may themselves induce metabolism and may reduce plasma concentrations of other drugs.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of HIV-protease inhibitors, including indinavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These include

- the alpha$_1$-adrenoceptor antagonist alfuzosin
- antiarrhythmics (amiodarone)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (alprazolam, oral midazolam, and triazolam)
- statins (lovastatin and simvastatin)

When indinavir is boosted with ritonavir, use with bepridil, clozapine, dextropropoxyphene, fusidic acid, diazepam, estazolam, flurazepam, quinidine, pethidine, and piroxicam should also be avoided. Similarly, ritonavir-boosted indinavir should not be used with drugs having narrow therapeutic windows that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics encainide, flecainide, and propafenone. Owing to the potential for increased serum concentrations of sildenafil, indinavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, indinavir may increase serum concentrations of inhaled salmeterol and the combination is not recommended. Use of indinavir with rosuvastatin should also be avoided. Rifampicin and St John's wort decrease the concentration of indinavir; use with the antiretroviral is contra-indicated due to the possible loss of its activity and development of resistance. Use of indinavir with atazanavir is contra-indicated as both drugs have been associated with indirect hyperbilirubinaemia.

Other HIV-protease inhibitors may have similar interactions. The principal interactions that have been reported as a risk for one or more of the various HIV-protease inhibitors are listed below.

References to interactions associated with HIV-protease inhibitors.

1. Eagling VA, *et al.* Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *Br J Clin Pharmacol* 1997; 44: 190–4.
2. von Moltke LL, *et al.* Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. *J Clin Pharmacol* 1998; 38: 106–11.
3. Malaty LI, Kuper JJ. Drug interactions of HIV protease inhibitors. *Drug Safety* 1999; 20: 147–69.
4. Jackson A, *et al.* Pharmacokinetics and pharmacodynamics of drug interactions involving HIV-1 protease inhibitors. *AIDS Rev* 2004; 6: 208–17.

Amfetamines. For mention of interactions, including a fatal serotonergic reaction, with *methylenedioxymethamfetamine* (Ecstasy) in patients receiving ritonavir, see p. 2325.3.

Analgesics. Ritonavir and possibly other HIV-protease inhibitors produce complex and potentially serious interactions with some opioids (see p. 111.2). Interactions between ritonavir and *dextropropoxyphene* (p. 45.1) or *pethidine* (p. 123.2) are considered to be especially hazardous. Ritonavir might also prolong *fentanyl*-induced respiratory depression (see p. 63.2). Amprenavir, nelfinavir, ritonavir, and ritonavir-boosted HIV-protease inhibitors may reduce plasma concentrations of *methadone* (see p. 91.1). For the effect of some HIV-protease inhibitors on the pharmacokinetics of *buprenorphine*, see p. 32.3.

Use of ritonavir with *piroxicam* can result in potentially toxic concentrations of piroxicam (see p. 126.3).

Antiarrhythmics. Use of HIV-protease inhibitors with the antiarrhythmics *amiodarone, encainide, flecainide, propafenone,* or *quinidine* may result in potentially toxic plasma concentrations of these drugs with an increased risk of ventricular arrhythmias.

Antibacterials. Plasma concentrations of HIV-protease inhibitors may be reduced to subtherapeutic levels by *rifampicin*; boosting with ritonavir does not overcome the interaction and increases the risk of hepatotoxicity.[1] *Rifabutin* generally has less effect but may reduce plasma concentrations of unboosted indinavir, saquinavir, and nelfinavir; conversely, it has been suggested that use of rifabutin may increase plasma concentrations of ritonavir-boosted lopinavir (see p. 1003.1). In addition, plasma concentrations of ritonavir-boosted rifabutin are generally increased by most HIV-protease inhibitors, with a consequent risk of uveitis. In general, HIV-protease inhibitors should not be used with rifampicin (p. 353.2) and dose reduction of rifabutin is generally required when it is given with an HIV-protease inhibitor (see under Uses and Administration of Rifabutin, p. 349.1). Increased doses of indinavir have been suggested for use with rifabutin, for details see Uses and Administration, p. 986.1.

HIV-protease inhibitors may inhibit the metabolism of *clarithromycin* (p. 267.3) and possibly other macrolides.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)

Antidepressants. HIV-protease inhibitors may inhibit the metabolism of *desipramine* and other tricyclic antidepressants (p. 406.3). Interactions may also occur between HIV-protease inhibitors and SSRIs such as *fluoxetine* (p. 424.3), and have also occurred with *bupropion* (p. 410.2) and *trazodone* (p. 452.2).

Plasma concentrations of HIV-protease inhibitors may be reduced by *St John's wort* as a result of induction of cytochrome P450; concomitant use should be avoided.[1] It should be noted that the inducing effect of St. John's wort may persist for at least 2 weeks after treatment is stopped.

1. Piscitelli SC, *et al.* Indinavir concentrations and St John's wort. *Lancet* 2000; 355: 547–8. Correction. *Ibid.* 2001; 357: 1210.

Antiepileptics. Reduced plasma concentrations of HIV-protease inhibitors may be anticipated if the enzyme inducers *carbamazepine, phenobarbital,* or *phenytoin* are given concurrently; in particular, once daily regimens of ritonavir-boosted lopinavir should be avoided with any of these drugs.[1]

Plasma concentrations of antiepileptics may also be altered when they are used with HIV-protease inhibitors. For further information, see under Carbamazepine (p. 517.2), Phenobarbital (p. 537.3), Phenytoin (p. 544.1), Lamotrigine (p. 530.2), and Valproate (p. 558.1).

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)

Antifungals. Plasma concentrations of HIV-protease inhibitors may be increased by azole antifungals. Reduced doses of indinavir have been recommended for use with *itraconazole*, and may also be considered for use with *ketoconazole*—for further information see under Uses and Administration (p. 986.1).

Conversely, plasma concentrations of ketoconazole, and possibly itraconazole may be increased by some HIV-protease inhibitors, and in particular ritonavir. US licensed product information for ritonavir advises that itraconazole or ketoconazole doses greater than 200 mg daily are not recommended. Similarly, *fluconazole* can cause significant increases in tipranavir concentrations, and it has therefore been suggested that if this combination is used, fluconazole doses should not exceed 200 mg daily. In contrast, HIV-protease inhibitors (and especially ritonavir) may substantially decrease concentrations of *voriconazole*; use with ritonavir or any ritonavir-boosted HIV-protease inhibitor should be avoided.

Antihistamines. HIV-protease inhibitors inhibit the metabolism of non-sedating antihistamines such as *astemizole* and *terfenadine* resulting in increased plasma concentrations of these drugs and an increased risk of serious ventricular arrhythmias. Such combinations should be avoided.

Antimalarials. For a discussion of possible interactions between HIV-protease inhibitors and *quinine*, see p. 668.1.

Antineoplastics. Plasma concentrations of indinavir were increased[1] during use with *interleukin-2*. Plasma concentrations of the vinca alkaloids, *vincristine* and *vinblastine*, (see p. 882.3) may also be increased when given with ritonavir, potentially leading to significant haematological or gastrointestinal adverse effects. For the effect of HIV-pro-

tease inhibitors on *paclitaxel*, see Interactions, Antivirals, p. 842.2.

1. Piscitelli SC, *et al.* Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. *Pharmacotherapy* 1998; **18**: 1212–16.

Antipsychotics. Ritonavir and possibly other HIV-protease inhibitors may increase plasma concentrations of *clozapine* (but see p. 1061.3), *pimozide* (p. 1097.2), and *sertindole* (p. 1107.3) resulting in increased toxicity. Concomitant use should be avoided. Plasma concentrations of *thioridazine* may also be increased when given with some HIV-protease inhibitors.

Antivirals. HIV-protease inhibitors can inhibit metabolism of other drugs from the same class[1] and increases in adverse effects have resulted.

Plasma concentrations of atazanavir, amprenavir/fosamprenavir, indinavir,[2] and lopinavir-ritonavir may be reduced by *nevirapine*; although increased doses of ritonavir-boosted lopinavir can be considered to manage the interaction (see under Uses and Administration of Lopinavir, p. 1002.1), licensed product information advises that use of atazanavir or unboosted fosamprenavir with nevirapine should be avoided.

Plasma concentrations of amprenavir/fosamprenavir, indinavir,[3] lopinavir, nelfinavir, ritonavir, and saquinavir may be increased by *delavirdine*; a decreased dose of indinavir is recommended when it is used with delavirdine (see Uses and Administration, p. 986.1) and the UK licensed information for saquinavir recommends that liver function should be monitored if saquinavir is given with delavirdine. Fosamprenavir and nelfinavir may in contrast decrease plasma concentrations of delavirdine (for further information see under Interactions of Delavirdine, p. 972.2).

Plasma concentrations of amprenavir/fosamprenavir, atazanavir, darunavir, indinavir, *lopinavir*, and saquinavir are decreased when given with *efavirenz*. Dose adjustments can be considered when efavirenz is used with ritonavir-boosted lopinavir, or in some cases, with ritonavir-boosted atazanavir; for further information, see Uses and Administration of Lopinavir (p. 1002.1) and Atazanavir (p. 968.1), respectively. The use of efavirenz with ritonavir is associated with an increased frequency of adverse effects, presumably due to competitive inhibition of metabolism, and liver enzymes should be monitored in patients receiving this combination. Plasma concentrations of nelfinavir are increased when given with efavirenz, but the combination is usually well tolerated at standard doses.

Plasma concentrations of HIV-protease inhibitors may also be altered by *etravirine*; use with certain HIV-protease inhibitors should be avoided entirely (see Interactions of Etravirine, p. 978.3).

Although there is no direct interaction between HIV-protease inhibitors and *didanosine*, the buffer included in the didanosine formulation can impair their absorption; doses should be separated by at least 1 to 2 hours from didanosine doses, which should be given on an empty stomach.

For a report of reduced area under the plasma concentration-time curve for *zidovudine* in patients receiving ritonavir, see p. 1026.3.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 04/04/11)
2. Murphy RL, *et al.* Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1. *J Infect Dis* 1999; **179**: 1116–23.
3. Perry JJ, *et al.* Pharmacokinetic drug-drug interaction study of delavirdine and indinavir in healthy subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18**: 252–9.

Benzodiazepines. For the effect of HIV-protease inhibitors on benzodiazepines, see Diazepam, p. 1069.2.

Cardiac glycosides. For details of a possible interaction between ritonavir and *digoxin*, see p. 1357.1.

Corticosteroids. Corticosteroids, in particular *dexamethasone*, may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations. For the effect of ritonavir on plasma concentrations of *fluticasone*, see p. 1620.1

Ergot alkaloids. For reports of ergotism in patients receiving HIV-protease inhibitors and ergotamine, see Ergotamine, p. 675.3.

Gastrointestinal drugs. The antidiarrhoeal *loperamide* markedly reduced exposure to saquinavir in 12 healthy subjects given a single dose of both drugs.[1] Exposure was reduced by about 54%, a reduction of the same order of magnitude as seen with enzyme inducers such as rifampicin, although the mechanism in this case was thought likely to be impaired absorption of the antiviral. Prolonged use of loperamide might lead to substantial reductions in saquinavir plasma concentrations, and reduced clinical efficacy. Plasma concentrations of loperamide were also increased, and those of its metabolite desmethylloperamide correspondingly reduced, but this was thought unlikely to be of clinical significance.

Atazanavir and indinavir depend on acid pH in the stomach for adequate absorption, and acid-suppressive therapies such as *histamine H_2-antagonists* and *proton pump inhibitors* may significantly reduce their absorption; if acid-suppressive therapy is necessary, it has been suggested that these HIV-protease inhibitors be boosted with low-dose ritonavir to ensure adequate antiretroviral activity.[2] In the case of atazanavir, a dose increase of the antiretroviral may also be necessary if use with an acid-suppressive therapy cannot be avoided; for further information, see Uses and Administration of Atazanavir (p. 968.1). A review[3] suggested a similar precaution (or giving the two drugs at suitably separated intervals) for fosamprenavir; there was conflicting evidence for a decrease in plasma concentrations of lopinavir and tipranavir with increased gastric pH and any clinical significance was uncertain. It considered that nelfinavir should not be given with a proton pump inhibitor.[3] A pharmacokinetic study in 12 patients with HIV reported an increased exposure to saquinavir when omeprazole was given with, or 2 hours before, a regular dose of ritonavir-boosted saquinavir. The mechanism for this interaction is unclear; inhibition of cytochrome P450 isoenzymes by omeprazole could play a role.[4] Licensed product information suggests caution when using omeprazole and ritonavir-boosted saquinavir together, and recommends monitoring for saquinavir toxicity.

For the effect of HIV-protease inhibitors on *cisapride*, see p. 1835.3.

1. Mikus G, *et al.* Reduction of saquinavir exposure by coadministration of loperamide: a two-way pharmacokinetic interaction. *Clin Pharmacokinet* 2004; **43**: 1015–24.
2. Fulco PP, *et al.* Acid suppressive therapy and the effects on protease inhibitors. *Ann Pharmacother* 2006; **40**: 1974–83.
3. Falcon RW, Kakuda TN. Drug interactions between HIV protease inhibitors and acid-reducing agents. *Clin Pharmacokinet* 2008; **47**: 75–89.
4. Singh K, *et al.* Pharmacokinetics and safety of saquinavir/ritonavir and omeprazole in HIV-infected subjects. *Clin Pharmacol Ther* 2008; **83**: 867–72.

Grapefruit. Exposure to saquinavir was increased by 50% when taken with grapefruit juice;[1] however, licensed product information does not recommend any adjustment of dosage of saquinavir.

1. Kupferschmidt HHT, *et al.* Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in men. *Br J Clin Pharmacol* 1998; **45**: 355–9.

Hormonal contraceptives. For the effect of HIV-protease inhibitors on the efficacy of hormonal contraceptives, see p. 2243.3.

Immunosuppressants. Mutual increases in the area under the plasma concentration-time curves for saquinavir and *ciclosporin* were reported in a kidney transplant recipient.[1] The resultant adverse effects subsided when doses of both drugs were reduced by half. Similar interactions have occurred with other HIV-protease inhibitors.

HIV-protease inhibitors may inhibit the metabolism of *tacrolimus* (see Antivirals, p. 1978.1).

1. Brinkman K, *et al.* Pharmacokinetic interaction between saquinavir and cyclosporine. *Ann Intern Med* 1998; **129**: 914–15.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals including indinavir, see Stavudine, p. 1016.2.

Statins. HIV-protease inhibitors may inhibit the metabolism of statins metabolised by CYP3A4 isoenzymes resulting in an increased risk of myopathy. Although those statins less dependent on CYP3A4 for metabolism may be used in certain circumstances to manage HIV-protease inhibitor-induced lipid disorders, in general use with lovastatin or simvastatin should be avoided, and HIV-protease inhibitors should be given with caution in patients receiving atorvastatin or rosuvastatin.

Theophylline. For a potential effect of ritonavir on theophylline, see p. 1235.2.

Urological drugs. Serum concentrations of the phosphodiesterase type-5 inhibitors *sildenafil*, *tadalafil*, and *vardenafil* may be increased when some HIV-protease inhibitors, particularly ritonavir, are given concurrently.

For the effect of HIV-protease inhibitors on sildenafil, including a report of fatal myocardial infarction after sildenafil in a patient receiving ritonavir and saquinavir, see p. 2366.3.

Where use of sildenafil, tadalafil, or vardenafil with a potent CYP3A4 inhibitor (such as indinavir or ritonavir) cannot be avoided, reduced doses have been suggested; use of HIV-protease inhibitors (particularly ritonavir) is contra-indicated in those using sildenafil for the treatment of pulmonary hypertension. For further information, see under Uses and Administration of Sildenafil (p. 2364.2) Tadalafil (p. 2368.2), and Vardenafil (p. 2372.1).

Vasopressin receptor antagonists. HIV-protease inhibitors may inhibit the metabolism of conivaptan (see p. 2486.2 and tolvaptan (see p. 2633.1).

Warfarin. For the effect of HIV-protease inhibitors on the response to warfarin and other anticoagulants, see p. 1533.1.

Antiviral Action

Indinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 proteases with a tenfold greater selectivity for HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Indinavir is rapidly absorbed after oral doses and peak plasma concentrations occur in 0.8 hours (range 0.5 to 1.1 hours). Bioavailability is about 65% after a single 800-mg dose. Absorption is reduced if given with a meal high in calories, fat, and protein but is less affected by a light meal (for the effect of pH see Gastrointestinal Drugs under Interactions, above). At doses up to 1 g, increases in plasma concentration are proportionately greater than increases in dose. Plasma protein binding is about 60%. Indinavir is reported to cross the blood-brain barrier. It undergoes oxidative metabolism by cytochrome P450 isoenzyme CYP3A4 and glucuronidation. At least seven metabolites (1 glucuronide and 6 oxidative metabolites) have been identified. The elimination half-life is 1.8 hours. Less than 20% of the absorbed dose is excreted in the urine, about half of this as unchanged drug. The remainder is excreted in the faeces.

References.
1. Ståhle L, *et al.* Indinavir in cerebrospinal fluid of HIV-1-infected patients. *Lancet* 1997; **350**: 1823.
2. Bernard L, *et al.* Indinavir concentrations in hair from patients receiving highly active antiretroviral therapy. *Lancet* 1998; **352**: 1757–8.
3. Wintergerst U, *et al.* Use of saliva specimens for monitoring indinavir therapy in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2000; **44**: 2572–4.
4. Haas DW, *et al.* Steady-state pharmacokinetics of indinavir in cerebrospinal fluid and plasma among adults with human immunodeficiency virus type 1 infection. *Clin Pharmacol Ther* 2000; **68**: 367–74.
5. Burger DM, *et al.* Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2001; **45**: 701–5.
6. Kappelhoff BS, *et al.* Population pharmacokinetics of indinavir alone and in combination with ritonavir in HIV-1-infected patients. *Br J Clin Pharmacol* 2005; **60**: 276–86.
7. Unadkat JD, *et al.* Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2007; **51**: 783–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avural; Crixivan; Elvenavir; Forli; Indilea†; Inhibisam†; ***Austral.***: Crixivan; ***Austria***: Crixivan; ***Belg.***: Crixivan; ***Braz.***: Crixivan; Indinax; ***Canad.***: Crixivan; ***Chile***: Crixivan; ***China***: Ai Hao (艾好); Crixivan (佳惠思); Ou Zhi (欧置); YouXin (又欣); ***Cz.***: Crixivan; ***Denm.***: Crixivan; ***Fin.***: Crixivan; ***Fr.***: Crixivan; ***Ger.***: Crixivan; ***Gr.***: Crixivan; ***Hong Kong***: Crixivan; ***Hung.***: Crixivan; ***India***: Inbec; Ind; Indease; Indivan; ***Irl.***: Crixivan; ***Israel***: Crixivan; ***Ital.***: Crixivan; ***Malaysia***: Crixivan; ***Mex.***: Aviran†; Crixivan; Indilan; ***Neth.***: Crixivan; ***Norw.***: Crixivan; ***NZ***: Crixivan; ***Philipp.***: Crixivan; ***Pol.***: Crixivan; ***Port.***: Crixivan; ***Rus.***: Crixivan (Криксивэн); ***S. Afr.***: Crixivan; ***Singapore***: Crixivan; ***Spain***: Crixivan; ***Swed.***: Crixivan; ***Switz.***: Crixivan; ***Thai.***: Crixivan†; Inavir; ***Turk.***: Crixivan; ***UK***: Crixivan; ***USA***: Crixivan; ***Venez.***: Crixivan; Indivan.

Inosine Pranobex *(BAN)*

Inosin Pranobeks; Inosina dimepranol acedobén; Inosina pranobex; Inosine Acédobène Diméprano!; Inosine Dimepranol Acedoben (pINNM); Inosinum Dimepranolum Acedobenum; Inosinum pranobexum; Inosiplex; Isoprinosine; Methisoprinol; Metisoprinol; NP-113; NPT-10381; Pranobeks Inozyny; Инозин Димепранол Ацедобен.

Inosine 2-hydroxypropyldimethylammonium 4-acetamidobenzoate (1:3).

$C_{10}H_{12}N_4O_5.C_{14}H_{22}N_2O_4$ (1:3)=1115.2

CAS — 36703-88-5.

ATC — J05AX05.

ATC Vet — QJ05AX05.

UNII — W1SO0V223F.

NOTE. Dimepranol Acedoben is *pINN* and *USAN*.

Uses and Administration

Inosine pranobex is a complex of inosine (p. 2533.1) with dimepranol acedoben ((±)-1-(dimethylamino)-2-propanol *p*-acetamidobenzoate). It has been used in the treatment of various viral infections, including herpes simplex (p. 955.2), genital warts (below), and subacute sclerosing panencephalitis (below), although other treatments or measures are preferred. The oral dose in mucocutaneous herpes simplex is 1 g four times daily for 7 to 14 days. An oral dose of 1 g three times daily is given for 14 to 28 days as an adjunct to standard topical treatment for genital warts. In subacute sclerosing panencephalitis, the oral dose is 50 to 100 mg/kg daily in divided doses given every 4 hours.

Reviews.

1. Campoli-Richards DM, *et al.* Inosine pranobex: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1986; 32: 383–424.

Alopecia. Oral inosine pranobex (50 mg/kg daily in 5 divided doses for 12 weeks) has been investigated[1] with some apparent benefit in the treatment of recalcitrant alopecia areata (p. 1682.3).

1. Georgala S, *et al.* Inosiplex for treatment of alopecia areata: a randomized placebo-controlled study. *Acta Derm Venereol* 2006; 86: 422–4.

Subacute sclerosing panencephalitis. Inosine pranobex has been tried[1,2] in the treatment of subacute sclerosing panencephalitis, a complication of measles (p. 961.2), but the results of clinical studies have been equivocal. Some success has been reported when inosine pranobex has been given with interferons and other antivirals. However, a randomised study involving 121 patients, of whom 67 completed analysis, was unable to show any difference between an oral regimen of inosine pranobex 100 mg/kg daily in 3 divided doses (up to a maximum of 3 g daily) for 6 months, and the same dose combined with intraventricular interferon alfa, although the outcomes, which were considered satisfactory in about 35% of cases, were better than the 10% remission rate in historical controls, implying some benefit with either treatment.[3]

1. Haddad FS, Risk WS. Isoprinosine treatment in 18 patients with subacute sclerosing panencephalitis: a controlled study. *Ann Neurol* 1980; 7: 185–8.
2. Jones CE, *et al.* Inosiplex therapy in subacute sclerosing panencephalitis: a multicentre, non-randomised study in 98 patients. *Lancet* 1982; i: 1034–7.
3. Gascon GG. International Consortium on Subacute Sclerosing Panencephalitis. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-α in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol* 2003; 18: 819–27. Correction. *ibid.* 2004; 19: 342.

Warts. Although of no apparent benefit in the treatment of palmar/plantar warts,[1] oral inosine pranobex has been shown to be of value in the treatment of refractory genital warts (p. 1689.3) in the cervix,[2] as well as producing some apparent epithelial morphological improvement in women with subclinical human papillomavirus infection of the vulva.[3]

1. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; 127: 262–5.
2. Georgala S, *et al.* Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial. *BJOG* 2006; 113: 1088–91.
3. Tay SK. Efficacy of inosine pranobex oral therapy in subclinical human papillomavirus infection of the vulva: a randomized double-blinded placebo controlled study. *Int J STD AIDS* 1996; 7: 276–80.

Adverse Effects and Precautions

Some patients have had transient nausea, vomiting, headaches, arthralgia, fatigue, vertigo, raised liver enzymes, pruritus, and rashes. Metabolism of the inosine content of inosine pranobex leads to increased serum and urine concentrations of uric acid; caution is therefore recommended in treating patients with renal impairment, gout, or hyperuricaemia.

Antiviral Action

Inosine pranobex appears to owe its activity in viral infections more to its capacity to modify or stimulate cell-mediated immune processes than to a direct action on the virus.

Pharmacokinetics

Inosine pranobex is reported to be rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 hour after an oral dose. It is also rapidly metabolised with a plasma half-life of 50 minutes, the inosine portion of the complex yielding uric acid; the other components undergo oxidation and glucuronidation. The metabolites are excreted in the urine.

References.

1. Nielsen P, Beckett AH. The metabolism and excretion in man of NN-dimethylamino-isopropanol and p-acetamido-benzoic acid after administration of isoprinosine. *J Pharm Pharmacol* 1981; 33: 549–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Isoprinosine; *Canad.*: Imunovir; *Chile*: Isoprinosine; *Cz.*: Isoprinosine; *Fr.*: Isoprinosine; *Ger.*: delimmun; Isoprinosine†; *Gr.*: Cicloxab; Iostop†; Isoprinosine; *Hong Kong*: Qualiprinol; *Hung.*: Isoprinosine; *Indon.*: Isoprinosine; Isprinol; *Irl.*: Imunovir†; Isoprinosine; *Ital.*: Viruxan; *Mex.*: Isoprinosine; Pranosine; *NZ*: Imunovir; *Philipp.*: Immunosin; Isoprinosine; *Pol.*: Groprinosin; Neosine; *Rus.*: Groprinosin (Гроприносин); Isoprinosine (Изопринозин); *Singapore*: Imin; *UK*: Imunovir; *Ukr.*: Groprinosin (Гроприносин); Isoprinosine (Изопринозин).

Multi-ingredient Preparations. *Philipp.*: Isoflu (Combipack).

Interferon Alfa *(BAN, rINN)*

IFN-α; Interferón-α; Interferon-α; Interferón alfa; Interféron Alfa; Interferon alpha; Interferoni Alfa; Interferonialfa; Interferonum Alfa; Ro-22-8181 (interferon alfa-2a); Sch-30500 (interferon alfa-2b); Интерферон Альфа.

CAS — 74899-72-2 (interferon alfa); 76543-88-9 (interferon alfa-2a); 99210-65-8 (interferon alfa-2b); 118390-30-0 (interferon alfacon-1); 198153-51-4 (peginterferon alfa-2a); 215647-85-1 (peginterferon alfa-2b).

ATC — L03AB01 (natural); L03AB04 (2a); L03AB05 (2b); L03AB06 (n1); L03AB09 (alfacon-1); L03AB10 (peginterferon alfa-2b); L03AB11 (peginterferon alfa-2a).

ATC Vet — QL03AB01 (natural); QL03AB04 (2a); QL03AB05 (2b); QL03AB06 (n1); QL03AB09 (alfacon-1); QL03AB10 (peginterferon alfa-2b); QL03AB11 (peginterferon alfa-2a).

UNII — 47RRR83SK7 (interferon alfa-2a); 43K1W2T1M6 (interferon alfa-2b).

NOTE. Interferon alfa was previously known as leucocyte interferon or lymphoblastoid interferon.

Interferon alfa-2a, alfa-2b, alfa-n1, and alfa-n3 are *USAN*.

Interferon alfacon-1 (*BAN, USAN, rINN*) is a recombinant non-naturally occurring alfa interferon. Peginterferon alfa-2a (*BAN, USAN, rINN*) and peginterferon alfa-2b (*BAN, rINN*) are interferons pegylated by conjugation with macrogols.

Pharmacopoeias. *Chin.* includes monographs for recombinant human alfa-2a and alfa-2b. *Eur.* (see p. vii) includes Interferon Alfa-2 Concentrated Solution.

Ph. Eur. 8: (Interferon Alfa-2 Concentrated Solution; Interferoni Alfa-2 Solutio Concentrata). It is produced by a method based on recombinant DNA technology using bacteria as host cells. A solution of a protein that is produced according to the information coded by the alfa-2 sub-species of interferon alfa gene. Interferon alfa-2a has a lysine residue at position 23 and interferon alfa-2b has an arginine residue. The concentrated solution contains a minimum of $2X10^8$ units/mL and has a minimum potency of $1.4X10^8$ units/mg of protein. A clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of -20 degrees or below. Protect from light.

Nomenclature. Interferon alfa may be derived from leucocytes or lymphoblasts, or produced by recombinant DNA technology. Sub-species of the human alfa gene may produce interferon alfa with protein variants or a mixture of proteins. The protein variants may be designated by a number (as in interferon alfa-2) which may be further qualified by a letter to indicate the amino-acid sequences at positions 23 and 34:

- interferon alfa-2a has lysine at 23 and histidine at 34
- interferon alfa-2b has arginine at 23 and histidine at 34
- interferon alfa-2c has arginine at both positions

In the case of a mixture of proteins an alphanumeric designation is given (as in interferon alfa-n1). Interferon alfacon-1 varies from interferon alfa-2 in 20 of 166 amino acids.

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology; (lns) indicates production by cultured lymphoblasts from the Namalwa cell line that have been stimulated by a Sendai virus; (bls) indicates production from leucocytes from human blood that have been stimulated by a Sendai virus.

References.

1. Finter NB. The naming of cats—and alpha-interferons. *Lancet* 1996; 348: 348–9.

Uses and Administration

The interferons are cytokines that have a range of activities. In addition to their action against viruses they are active against malignant neoplasms and have an immunomodulating effect. Several alfa interferons are available: interferon alfa-2a (rbe), interferon alfa-2b (rbe), alfa-n3 (bls), alfacon-1 (rbe), and the pegylated interferons peginterferon alfa-2a (rbe) and peginterferon alfa-2b (rbe).

Alfa interferons are used in chronic hepatitis B and chronic hepatitis C; in several malignant neoplasms including AIDS-related Kaposi's sarcoma, hairy-cell leukaemia, chronic myeloid leukaemia, follicular lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, melanoma, multiple myeloma, and renal cell carcinoma, and in condylomata acuminata.

ADMINISTRATION AND DOSAGE. Dosage regimens for alfa interferons are as follows:

- **Chronic active hepatitis B.** *Interferon alfa-2a* is given in a dose of 2.5 to 5 million units/m² three times weekly by subcutaneous injection for 4 to 6 months. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously for 48 weeks. *Interferon alfa-2b* is given in a dose of 5 to 10 million units three times weekly for 4 to 6 months, or 5 million units daily for 16 weeks, by subcutaneous or intramuscular injection.
- **Chronic hepatitis C.** *Interferon alfa-2a* is given in a dose of 3 to 4.5 million units three times weekly by subcutaneous injection for 6 months when it is used with ribavirin. In patients unable to tolerate ribavirin, interferon alfa-2a monotherapy is given either in an initial dose of 3 to 6 million units three times weekly for 6 months followed by 3 million units three times weekly for an additional 6 months, or in a dose of 3 million units three times weekly for 12 months, by subcutaneous injection. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously, with ribavirin or as monotherapy, for 24 to 48 weeks (depending on genotype). *Interferon alfa-2b* is given in a dose of 3 million units three times weekly for 6 to 12 months (depending on genotype) with ribavirin or, when given as monotherapy, for 6 to 18 months, or for up to 24 months (depending on genotype), by subcutaneous or intramuscular injection. *Peginterferon alfa-2b* is given subcutaneously in a dose of 1.5 micrograms/kg once weekly for 24 to 48 weeks with ribavirin, or in a dose of 0.5 or 1 microgram/kg once weekly for 24 to 48 weeks when given as monotherapy. *Interferon alfacon-1* is given in a dose of 9 micrograms three times weekly by subcutaneous injection for 24 weeks followed by 15 micrograms three times weekly for up to 48 weeks if necessary.

  For information on the dose of ribavirin used in the treatment of chronic hepatitis C see under Ribavirin, p. 1010.2.
- **AIDS-related Kaposi's sarcoma.** *Interferon alfa-2a* is usually given in an escalating dose of 3 million units daily for 3 days, 9 million units daily for 3 days, 18 million units daily for 3 days, and 36 million units daily, if tolerated, on days 10 to 84, by subcutaneous injection; thereafter the maximum tolerated dose (up to 36 million units) may be given three times weekly. *Interferon alfa-2b* is given in a dose of 30 million units/m² three times weekly, by subcutaneous or intramuscular injection.
- **Hairy-cell leukaemia.** *Interferon alfa-2a* is given in an initial subcutaneous dose of 3 million units daily for 16 to 24 weeks, then the same dose three times weekly, by subcutaneous injection. Treatment has continued for up to 24 months. *Interferon alfa-2b* is given in a dose of 2 million units/m² three times weekly by subcutaneous or intramuscular injection for up to 6 months or more.
- **Chronic myeloid leukaemia.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, 6 million units daily for 3 days, and 9 million units daily thereafter. Patients showing a response after 12 weeks should continue treatment until a complete haematological response is achieved or for a maximum of 18 months; those who achieve a complete haematological response should continue on 9 million units daily (or a minimum of 9 million units three times weekly) in order to achieve a cytogenetic response. *Interferon alfa-2b* is given in a dose of 4 to 5 million units/m² daily by subcutaneous injection, continuing at the maximum tolerated dose to maintain remission (usually 4 to 5 million units/m² daily).
- **Follicular lymphoma.** *Interferon alfa-2a* is given as an adjunct to chemotherapy in a dose of 6 million units/m² daily by subcutaneous injection on days 22 to 26 of each 28-day chemotherapy cycle. *Interferon alfa-2b* is given as an adjunct to chemotherapy in a dose of 5 million units three times weekly by subcutaneous injection for 18 months.
- **Cutaneous T-cell lymphoma.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, then 9 million units daily for 3 days, and then 18 million units daily to complete 12 weeks of treatment. The maximum tolerated dose (up to 18 million units) is then given three times weekly for a minimum of 12 months in responding patients.
- **Carcinoid tumours.** *Interferon alfa-2b* is given in a dose of 3 to 9 million units (usually 5 million units) three times

weekly by subcutaneous injection. In advanced disease, 5 million units may be given daily.

- **Melanoma.** *Interferon alfa-2a* is given in a dose of 3 million units three times weekly by subcutaneous injection for 18 months. Treatment should start no later than 6 weeks after surgery. *Interferon alfa-2b* is given in an initial dose of 20 million units/m² daily on 5 days each week for 4 weeks by intravenous infusion over 20 minutes, and then for maintenance 10 million units/m² three times weekly by subcutaneous injection for 48 weeks. *Peginterferon alfa-2b* is given as adjuvant treatment in an initial dose of 6 micrograms/kg once weekly by subcutaneous injection for 8 doses, followed by a maintenance dose of 3 micrograms/kg once weekly by subcutaneous injection for up to 5 years.
- **Multiple myeloma.** *Interferon alfa-2b* is given as maintenance treatment following chemotherapy induction at a dose of 3 million units/m² three times weekly by subcutaneous injection.
- **Renal cell carcinoma.** *Interferon alfa-2a* is given as an adjunct to cytotoxic chemotherapy (vinblastine) in an escalating dose of 3 million units three times weekly for one week, then 9 million units three times weekly for one week, then 18 million units three times weekly thereafter for 3 to 12 months, by subcutaneous injection; if tolerance is poor, the dose may subsequently be reduced to 9 million units three times weekly. As an adjunct to bevacizumab, *interferon alfa-2a* may be given at a dose of 9 million units subcutaneously three times weekly (following a dose escalation period, if required, of not more than 2 weeks). Treatment may be continued until disease progression, or up to a maximum of 12 months. If tolerance is poor, the dose may be reduced to a minimum of 3 million units three times weekly.
- **Condylomata acuminata.** *Interferon alfa-2b* is given in a dose of 1 million units injected into each lesion three times weekly for 3 weeks, and repeated after 12 to 16 weeks if necessary. No more than 5 lesions should be treated in each treatment course. *Interferon alfa-n3* is given in a dose of 0.25 million units per lesion twice weekly for up to 8 weeks, to a maximum of 2.5 million units in each session.

See below for further details of these as well as some other uses of alfa interferons.

General reviews of interferons.

1. Volz MA, Kirkpatrick CH. Interferons 1992: how much of the promise has been realised? *Drugs* 1992; 43: 285–94.
2. Dorr RT. Interferon-α malignant and viral diseases: a review. *Drugs* 1993; 45: 177–211.
3. Haria M, Benfield P. Interferon-α -2a: a review of its pharmacological properties and therapeutic use in the management of viral hepatitis. *Drugs* 1995; 50: 873–96.
4. Ruszczak Z, Schwartz RA. Interferons in dermatology: biology, pharmacology, and clinical applications. *Adv Dermatol* 1997; 13: 235–88.
5. Edwards L. The interferons. *Dermatol Clin* 2001; 19: 139–46, ix.
6. Moschos S, *et al*. Interferons in the treatment of solid tumors. *Cancer Treat Res* 2005; 126: 207–41.
7. Pestka S. The interferons: 50 years after their discovery, there is much more to learn. *J Biol Chem* 2007; 282: 20047–51.
8. Priedman RM. Clinical uses of interferons. *Br J Clin Pharmacol* 2008; 65: 158–62.
9. Antonelli G. Biological basis for a proper clinical application of alpha interferons. *New Microbiol* 2008; 31: 305–18.
10. Fensterl V, Sen GC. Interferons and viral infections. *Biofactors* 2009; 35: 14–20.
11. Keating GM. Peginterferon-α -2a (40 kD): a review of its use in chronic hepatitis B. *Drugs* 2009; 69: 2633–60.
12. Foster GR. Pegylated interferons for the treatment of chronic hepatitis C: pharmacological and clinical differences between peginterferon-α -2a and peginterferon-α -2b. *Drugs* 2010; 70: 147–65.

Administration in children. Interferon alfa products are licensed in some countries for use in children for the treatment of chronic hepatitis B and chronic hepatitis C; they should always be used under the close supervision of a specialist. For information on the use of interferon alfa for the treatment of haemangiomas in children, see below.

Chronic hepatitis B

In the USA interferon alfa-2b (*Intron A; Schering-Plough*) is licensed for the treatment of chronic hepatitis B. The indication is based on a study in children from 1 to 17 years of age. The dose (based on body surface area) given by subcutaneous injection was 3 million units/m² three times a week for the first week of therapy followed by a dose increase to 6 million units/m² three times a week (to a maximum of 10 million units three times a week).

Treatment for chronic hepatitis B is usually given for 4 to 6 months.

Chronic hepatitis C

Interferon and peginterferon alfa-2b may be used in children from 3 to 17 years of age, with ribavirin, for the treatment of chronic hepatitis C. Duration of treatment may be influenced by the genotype of the hepatitis C virus. In hepatitis C mono-infection, patients with viral genotype 1 should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks. The recommended doses are based on body-surface; for interferon alfa-2b 3 million units/m² given subcutaneously 3 times a week while the dose for peginterferon alfa-2b is 60 micrograms/m² given subcutaneously once a week.

For information on the dose of ribavirin used in the treatment of chronic hepatitis C in children see under Ribavirin, p. 1010.3.

Age-related macular degeneration. In age-related macular degeneration (senile macular degeneration), a common cause of visual impairment in the elderly, there is a gradual and progressive deterioration of central vision usually affecting both eyes (p. 880.2). Despite encouraging preliminary results[1-4] with interferon alfa, controlled data showed no benefit after treatment for a year.[5]

1. Fine SL, *et al*. Age-related macular degeneration. *N Engl J Med* 2000 342: 483–92.
2. Arnold JJ, Sarks SH. Extracts from "clinical evidence": age related macular degeneration. *BMJ* 2000321: 741–4.
3. Comer GM, *et al*. Current and future treatment options for nonexudative and exudative age-related macular degeneration. *Drugs Aging* 200421: 967–92.
4. Sun JK, Miller JW. Medical treatment of choroidal neovascularization secondary to age-related macular degeneration. *Int Ophthalmol Clin* 200549: 115–32.
5. Pharmacological Therapy for Macular Degeneration Study Group. Interferon alfa-2a is ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective randomized placebo-controlled clinical trial. *Arch Ophthalmol* 1997: 115: 865–72.

Angiomatous disease. Encouraging responses were reported in 4 of 5 children treated with interferon alfa-2a for various angiomatous diseases.[1] Regression of haemangioma size by more than 50% was achieved in 11 of 18 infants and children given interferon alfa-2a for 1 to 5 months,[2] and in 11 of 19 children treated for at least 4 months.[3] Interferon alfa-2b has also been found to cause regression of haemangioma in 27 of 38 children treated for at least 6 months.[4] In addition, there have been reports of the successful use of interferon alfa-2b to treat infantile giant cell angioblastoma[5] and pelvic metastases of adult haemangioendothelioma of the liver.[6]

The use of interferons as anti-angiogenic agents has been reviewed.[7]

1. White CW, *et al*. Treatment of childhood angiomatous diseases with recombinant interferon alfa-2a. *J Pediatr* 1991: 118: 59–66.
2. Deb G, *et al*. Treatment of hemangiomas of infants and babies with interferon alfa-2a: preliminary results. *Int J Pediatr Hematol/Oncol* 1996; 3: 109–13.
3. Greinwald JH, *et al*. An update on the treatment of hemangiomas in children with interferon alfa-2a. *Arch Otolaryngol Head Neck Surg* 1999; 125: 21–7.
4. Garmendia G, *et al*. Regression of infancy hemangiomas with recombinant IFN-α 2b. *J Interferon Cytokine Res* 2001; 21: 31–8.
5. Marler JJ, *et al*. Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of 2 cases. *Pediatrics* 2002; 109: e37. Also available at: http://pediatrics.aappublications.org/cgi/content/full/109/2/e37 (accessed 12/06/08)
6. Kayler LK, *et al*. Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. *Transplantation* 2002; 74: 128–30.
7. Lindner DJ. Interferons as antiangiogenic agents. *Curr Oncol Rep* 2002; 4: 510–14.

Behçet's syndrome. Behçet's syndrome (p. 1601.1) is a systemic inflammatory disorder characterised by recurrent attacks of oral aphthous ulcers, genital ulcers, skin lesions, uveitis or other manifestations affecting the blood vessels, gastrointestinal tract, and respiratory and central nervous systems. Treatment is essentially symptomatic and empirical. A review of the literature[1] identified 338 patients who had been given interferon alfa (264 patients had received interferon alfa-2a and 74 interferon alfa-2b). Mucocutaneous symptoms improved in 86% of the patients; articular manifestations were present in 90 patients and 95% of them showed a partial or complete response to interferon alfa treatment. Ocular manifestations were present in 182 patients and 94% of them showed a partial or complete response to treatment.[1] Maximum response has been seen about 2 to 4 months after starting treatment.[2] Higher doses have been found to be more effective than low-dose regimens,[1,2] but the optimum duration of therapy remains to be determined. The best results were seen in patients with severe or refractory ocular disease.[2] Another review[3] on the management of Behçet's syndrome reported that treatment with interferon-alfa during an inflammatory attack improved the duration of and pain associated with oral aphthous ulcers; beneficial effects were also reported in patients with ocular manifestations. Randomised, controlled studies had shown that interferon alfa prevented recurrent attacks and it was considered to be effective in suppressing more severe systemic features, as well as mucocutaneous ones. Open studies with interferon alfa indicated that it might be of benefit in patients with disease resistant to conventional immunosuppressive treatments.

1. Kötter I, *et al*. The use of interferon alpha in Behçet disease: review of the literature. *Semin Arthritis Rheum* 2004; 33: 320–35.
2. Yang DS, *et al*. Interferon-alpha in the management of patients with Behçet's disease. *Br J Hosp Med* 2008; 69: 575–9.
3. Gul A. Standard and novel therapeutic approaches to Behçet's disease. *Drugs* 2007; 67: 2013–22.

Blood disorders. Interferon alfa may be used in the management of the myeloproliferative disorders such as *primary (essential) thrombocythaemia*[1-4] (p. 695.2), *polycythaemia vera*,[1-5] (p. 695.2) and *agnogenic myeloid metaplasia*.[2] Benefit has also been reported with interferon alfa in patients with HIV-associated thrombocytopenia,[6] although interferons have been reported to induce immune thrombocytopenia, and there has been a report of bleeding in a patient with this condition (see Effects on the Blood under Adverse Effects, p. 992.3).

In addition to case reports of interferon alfa producing improvements in patients with idiopathic *hypereosinophilic syndrome*[7-9] who had not responded to corticosteroids or hydroxycarbamide, studies have also shown beneficial responses to interferon alfa used alone[10] or with corticosteroids or hydroxycarbamide.[11,12]

See also under Malignant Neoplasms, p. 991.3.

Paradoxically, interferon alfa has also been used with some success in patients with *thrombocytopenia* associated with hepatitis C.[13-15]

1. Elliott MA, Tefferi A. Interferon-alpha therapy in polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost* 1997; 23: 463–72.
2. Radin AI, *et al*. Eastern Cooperative Oncology Group. Phase II study of alpha2 interferon in the treatment of the chronic myeloproliferative disorders (E5487): a trial of the Eastern Cooperative Oncology Group. *Cancer* 2003; 98: 100–109.
3. Jabbour E, *et al*. PEG-IFN-alpha-2b therapy in BCR-ABL-negative myeloproliferative disorders: final result of a phase 2 study. *Cancer* 2007; 110: 2012–18.
4. Quintás-Cardama A, *et al*. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol* 2009; 27: 5418–24.
5. Lengfelder E, *et al*. Interferon alpha in the treatment of polycythemia vera. *Ann Hematol* 2000; 79: 103–9.
6. Marroni M, *et al*. Interferon-α is effective in the treatment of HIV-1-related, severe, zidovudine-resistant thrombocytopenia. *Ann Intern Med* 1994; 121: 423–9.
7. Zielinski RM, Lawrence WD. Interferon-α for the hypereosinophilic syndrome. *Ann Intern Med* 1990; 113: 716–18.
8. Busch FW, *et al*. Alpha-interferon for the hypereosinophilic syndrome. *Ann Intern Med* 1991; 114: 338–9.
9. Yoon T-Y, *et al*. Complete remission of hypereosinophilic syndrome after interferon-α therapy: report of a case and literature review. *J Dermatol* 2000; 27: 110–15.
10. Butterfield JH, Gleich GJ. Interferon-α treatment of six patients with the idiopathic hypereosinophilic syndrome. *Ann Intern Med* 1994; 121: 648–53.
11. Coutant G, *et al*. Traitement des syndromes hyperéosinophiliques à expression myeloproliferative par l'association hydroxyurée-interféron alpha. *Ann Med Interne (Paris)* 1993; 144: 243–50.
12. Baratta L, *et al*. Favorable response to high-dose interferon-alpha in idiopathic hypereosinophilic syndrome with restrictive cardiomyopathy: case report and literature review. *Angiology* 2002; 53: 465–70.
13. Uygun A, *et al*. Interferon treatment for thrombocytopenia associated with chronic HCV infection. *Int J Clin Pract* 2000; 54: 683–4.
14. Rajan S, Liebman HA. Treatment of hepatitis C related thrombocytopenia with interferon alpha. *Am J Hematol* 2001; 68: 202–9.
15. Benci A, *et al*. Thrombocytopenia in patients with HCV-positive chronic hepatitis: efficacy of leucocyte interferon-α treatment. *Int J Clin Pract* 2003; 57: 17–19.

Churg-Strauss syndrome. For reports that interferon alfa may be beneficial in Churg-Strauss syndrome, see p. 1603.1.

Hepatitis. Interferon alfa (including peginterferon alfa) is one of the main drugs used in the treatment of viral hepatitis B and C and chronic hepatitis B and C co-infection with HIV (p. 952.1).

Interferon alfa was the first drug approved for the management of chronic **hepatitis B**. A meta-analysis[1] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HbeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels. Studies have suggested that subcutaneous peginterferon alfa is as effective or slightly more effective than interferon alfa given subcutaneously.[2] Results from various studies[3] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[4] and HBeAg-negative patients with chronic hepatitis B,[5] when peginterferon alfa was given subcutaneously, once weekly for 48 weeks. However, the addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[5,6] Interferon alfa can produce benefit in some patients co-infected with chronic **hepatitis B and D**.[7] However, these co-infected patients are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[7] with high-dose interferon alfa-2a (9 million units) given intramuscularly 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[8]

The first available treatment for **chronic hepatitis C** was interferon alfa-2b, and this was followed by interferon

alfa-2a, given subcutaneously 3 times a week. A meta-analysis[9] of studies involving interferon treatment of hepatitis C suggested that treatment with interferon alfa 3 million units three times weekly for at least 12 months had the best risk-benefit ratio for patients with chronic hepatitis C. Studies[10,11] with once-weekly peginterferon alfa showed it to be more effective than interferon alfa given three times weekly in patients with chronic hepatitis C, including those with cirrhosis or extensive fibrosis.[12]

Combination therapy with interferon alfa and oral ribavirin for the treatment of chronic hepatitis C is more effective than either drug alone with sustained responses having been recorded.[13] Meta-analyses have also concluded that the combination is more effective both in patients who had failed to respond to interferon alone or to other previous treatment,[14] and in patients with milder disease.[15] There is good evidence[16-18] that combining ribavirin with peginterferon alfa may be more effective than combination with interferon alfa. The British Society for Gastroenterology[19] and the American Association for the Study of Liver Diseases (AASLD)[20] therefore recommend weekly subcutaneous peginterferon alfa with daily oral ribavirin as the first choice of treatment for chronic hepatitis C. However, some have questioned whether this is true for all genotypes of the virus, suggesting that the benefit of peginterferon alfa is largely confined to patients with the less responsive genotype 1, rather than patients infected with genotypes 2 or 3.[21] (One study[16] suggested a sustained virological response (SVR) of around 42% in patients with genotype 1, versus about 80% with genotypes 2 and 3.) Rates of sustained virologic response and tolerability did not differ significantly between peginterferon alfa-2a and -2b (both given with ribavirin) in a study in patients with genotype 1 infection, treated for 48 weeks.[22]

Guidelines for the management of **HIV and hepatitis B** co-infection have been developed by various expert groups.[23-25] In patients not requiring HIV therapy peginterferon alfa for 12 months is considered an option for non-cirrhotic HBeAg-positive patients.[23] Treatment of **HIV and hepatitis C** co-infected patients has been associated with a high rate of intolerance and a low rate of response. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[26-28] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[26,28] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[27] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[27,28] Guidelines for the treatment and management of HIV and hepatitis C co-infection have been developed by various expert groups.[20,23,25,29] In general, they all recommend combination therapy with peginterferon alfa and ribavirin usually for 48 weeks. For further discussion on the management of chronic hepatitis B and C patients co-infected with HIV, see p. 952.1.

Although antivirals are generally not required in **acute hepatitis**, treatment of acute hepatitis C with interferon alfa has been shown to produce more rapid resolution of viraemia[30] and may decrease the risk of chronic hepatitis developing.[31] Studies[32] with peginterferon alfa-2b, in a small number of patients with acute hepatitis C, have shown similar efficacy. The AASLD[20] recommends that either interferon or peginterferon alfa given for a period of at least 6 months should be considered for the treatment of acute hepatitis C if the infection persists 2 to 4 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[33] and by the Scottish Intercollegiate Guidelines Network.[29]

1. Wong DKH, *et al.* Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B: a meta-analysis. *Ann Intern Med* 1993; 119: 312–23.
2. Lok ASF, McMahon BJ. American Association for the Study of Liver Diseases. Chronic hepatitis B: update 2009. *Hepatology* 2009; 50: 661–2. Full version: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf (accessed 17/08/10)
3. Marcellin P, *et al.* Treatment of chronic hepatitis B. *J Viral Hepatitis* 2005; 12: 333–45.
4. Lau GKK, *et al.* Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; 352: 2682–95.
5. Marcellin P, *et al.* Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; 351: 1206–17.
6. Janssen HLA, *et al.* Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005; 365: 123–9.
7. Farci P, *et al.* Treatment of chronic hepatitis D with interferon alfa-2a. *N Engl J Med* 1994; 330: 88–94.
8. Farci P, *et al.* Long-term benefit of interferon α therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology* 2004; 126: 1740–9.
9. Poynard T, *et al.* Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996; 24: 778–89.
10. Zeuzem S, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000; 343: 1666–72.
11. Perry CM, Jarvis B. Peginterferon-α -2a (40 kD): a review of its use in the management of chronic hepatitis C. *Drugs* 2001; 61: 2263–88.
12. Heathcote EJ, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000; 343: 1673–80.
13. Brok J, *et al.* Ribavirin plus interferon versus interferon for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 21/01/10).
14. Cummings KJ, *et al.* Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C previously nonresponsive to interferon: a meta-analysis of randomized trials. *JAMA* 2001; 285: 193–9.
15. Hartwell D, Shepherd J. Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and meta-analysis. *Int J Technol Assess Health Care* 2009; 25: 56–62.
16. Manns MP, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958–65.
17. Fried MW, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–82.
18. Simin M, *et al.* Cochrane systematic review: pegylated interferon plus ribavirin vs. interferon plus ribavirin for chronic hepatitis C. *Aliment Pharmacol Ther* 2007; 25: 1153–62.
19. Cramp M, Rosenberg W. British Society for Gastroenterology: guidance on the treatment of hepatitis C incorporating the use of pegylated interferons. 2003. Available at: http://www.bsg.org.uk/pdf_word_docs/pegylated_2003.doc (accessed 13/06/08)
20. Ghany MG, *et al.*, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; 49: 1335–74. Also available at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Diagnosis_of_HEP_C_Update.Aug_09pdf.pdf (accessed 17/08/10)
21. Jamall IS, *et al.* Is pegylated interferon superior to interferon, with ribavarin, in chronic hepatitis C genotypes 2/3? *World J Gastroenterol* 2008; 14: 6627–31.
22. McHutchison JG, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361: 580–93. Correction. *ibid.*: 1027.
23. Brook G, *et al.* British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. *HIV Med* 2010; 11: 1–30. Also available at: http://www.bhiva.org/documents/Guidelines/HepBC/2010/hiv_781.pdf (accessed 17/08/10)
24. Soriano V, *et al.* Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *AIDS* 2005; 19: 221–40. Correction. *ibid.*: 640.
25. Alberti A, *et al.* Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005; 42: 615–24. Correction. *ibid.*; 43: 1098.
26. Carrat F, *et al.* Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004; 292: 2839–48.
27. Torriani FJ, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351: 438–50.
28. Chung RT, *et al.* Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; 351: 451–9.
29. Scottish Intercollegiate Guidelines Network. Management of hepatitis C: a national clinical guideline (issued December 2006). Available at: http://www.sign.ac.uk/pdf/sign92.pdf (accessed 13/06/08)
30. Myers RP, *et al.* Interferon for acute hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/08).
31. Jaeckel E, *et al.* Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; 345: 1452–7.
32. Santantonio T, *et al.* Efficacy of a 24-week course of PEG-interferon α -2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 2005; 42: 329–33.
33. Clinical Effectiveness Group (British Association of Sexual Health and HIV). United Kingdom national guideline on the management of the viral hepatitides A, B & C 2008. Available at: http://www.bashh.org/documents/1927 (accessed 02/11/09)

Herpes simplex infections. Herpes simplex infections are commonly treated with aciclovir (see p. 955.2), but beneficial responses to topical interferon alfa have been reported in genital herpes, although results are mixed.[1] Interferon alfa has also been reported to have benefit in the treatment of herpes keratitis. A systematic review[2] of interventions for herpes simplex epithelial keratitis found that interferon monotherapy had a slightly beneficial effect on dendritic epithelial keratitis, but no more than that of other antivirals and concluded that the use of an antiviral nucleoside with interferon seemed to speed healing.

1. Leung DT, Sacks SL. Current recommendations for the treatment of genital herpes. *Drugs* 2000; 60: 1329–52.
2. Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 15/03/11).

HIV infection and AIDS. Interferons have been tried with some success in the management of Kaposi's sarcoma and mycobacterial infections in patients with AIDS (see below and under Interferon Gamma, p. 999.2, respectively).

Inflammatory bowel disease. Interferon alfa is one of many drugs that have been tried in inflammatory bowel disease (p. 1811.3). A study[1] found that clinical remission was achieved in 26 of 28 patients with ulcerative colitis after 6 to 12 months of treatment with interferon alfa-2a. Partial remission was reported in 2 of 5 patients with Crohn's disease[2] given interferon alfa, but in another study in 12 patients[3] interferon alfa was of no benefit. Although some results with interferon beta suggest benefit in the treatment of ulcerative colitis unresponsive to corticosteroids,[4,5] a controlled study with interferon beta-1a in patients with moderately active disease did not find any significant benefit.[6]

1. Sümer N, Palabiyikoğlu M. Induction of remission by interferon-α in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol* 1995; 7: 597–602.
2. Davidsen B, *et al.* Tolerability of interferon alpha-2b, a possible new treatment of active Crohn's disease. *Aliment Pharmacol Ther* 1995; 9: 75–9.
3. Gasché C, *et al.* Prospective evaluation of interferon-α in treatment of chronic active Crohn's disease. *Dig Dis Sci* 1995; 40: 800–4.
4. Musch E, *et al.* Induction and maintenance of clinical remission by interferon-β in patients with steroid-refractory active ulcerative colitis—an open long-term pilot trial. *Aliment Pharmacol Ther* 2002; 16: 1233–9.
5. Musch E, *et al.* Successful treatment of steroid refractory active ulcerative colitis with natural interferon-β —an open long-term trial. *Z Gastroenterol* 2007; 45: 1235–40.
6. Pena-Rossi C, *et al.* Clinical trial: a multicentre, randomized, double-blind, placebo-controlled, dose-finding, phase II study of subcutaneous interferon-β -1a in moderately active ulcerative colitis. *Aliment Pharmacol Ther* 2008; 28: 758–67.

Kaposi's sarcoma. The various treatments used for Kaposi's sarcoma, including the role of HAART as first-line therapy in the AIDS-related form, are discussed on p. 718.1. Interferon alfa has been used in AIDS-related Kaposi's sarcoma and in patients with the classical, nonepidemic form. In patients with AIDS-related Kaposi's sarcoma interferon alfa, either as monotherapy or with zidovudine, has shown benefit in HIV-positive patients provided they possess relatively elevated CD4+ T lymphocyte counts (greater than 150 cells/microlitre),[1] although other drugs have generally replaced interferon alfa as treatment for Kaposi's sarcoma.[2] Systemic and local therapy such as interferon alfa and chemotherapy may be combined with HAART.[3]

1. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist* 2001; 6: 34–55.
2. Krown SE. AIDS-associated Kaposi's sarcoma: is there still a role for interferon alfa? *Cytokine Growth Factor Rev* 2007; 18: 395–402.
3. Aldenhoven M, *et al.* Therapeutic strategies for epidemic Kaposi's sarcoma. *Int J STD AIDS* 2006; 571–8.

Malignant neoplasms. Many reports have been published on the effects of interferons on various neoplasms; most have involved interferon alfa.

Interferons have become established in the treatment of a few malignant disorders, notably hairy-cell leukaemia (but see p. 694.3), Kaposi's sarcoma (see above), and chronic myeloid leukaemia (p. 694.2). Alfa interferons may improve the duration of remission in multiple myeloma,[1-4] but not necessarily survival.[2,5] Combination therapy including interferons has also been used in indolent low-grade non-Hodgkin's lymphoma (p. 696.3) and interferon alfa has been used alone to maintain remission. In renal cell carcinoma (p. 708.3) response to interferon alfa used with interleukin-2 has been promising, but toxicity high; interferon alfa alone produces very modest benefit.[6] Very modest improvements in survival have been seen when interferon alfa was combined with bevacizumab.[7,8] Interferon alfa is also used in other neoplasms including melanoma (p. 714.3); neuroendocrine tumours[9] (p. 716.3); myelodysplasia; cutaneous T cell lymphomas including mycosis fungoides (p. 698.3); and in meningioma.[10,11] Interferons have been given locally as an adjunct to surgery for superficial bladder tumours (p. 700.2) and intralesionally or perilesionally in basal cell carcinoma[12-14] and also for keloid scars.[15,16] They may be used as an adjunct to curative therapy for hepatocellular carcinoma in patients with viral hepatitis.[17] Use of interferon alfa with fluorouracil has been tried in inoperable colorectal cancer but does not appear to be more beneficial than fluorouracil alone.[18] Interferon alfa given with zidovudine has produced encouraging results in adult T-cell leukaemia/lymphoma.[19] Peginterferon alfa has also been shown to be effective in the management of chronic myeloid leukaemia and solid tumours, including metastatic melanoma and renal cell carcinoma.[20]

1. Mandelli F, *et al.* Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 1990; 322: 1430–4.
2. Nordic Myeloma Study Group. Interferon-α 2b added to melphalan-prednisone for initial and maintenance therapy in multiple myeloma: a randomized, controlled trial. *Ann Intern Med* 1996; 124: 212–22.
3. Fritz E, Ludwig H. Interferon-α treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Ann Oncol* 2000; 11: 1427–36.
4. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. *Br J Haematol* 2001; 113: 1020–34.
5. Österborg A, *et al.* Natural interferon-α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: a randomized study from the myeloma group of central Sweden. *Blood* 1993; 81: 1428–34.
6. Medical Research Council Renal Cancer Collaborators. Interferon-α and survival in metastatic renal carcinoma: early results of a randomised controlled study. *Lancet* 1999; 353: 14–17.

7. Rini BI, *et al.* Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol* 2010; **28:** 2137–43.
8. Escudier B, *et al.* Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol* 2010; **28:** 2144–50.
9. Kölby L, *et al.* Randomized clinical trial of the effect of interferon α on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg* 2003; **90:** 687–93.
10. Wöber-Bingöl Ç, *et al.* Interferon-alfa-2b for meningioma. *Lancet* 1995; **345:** 331.
11. Kaba SE, *et al.* The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery* 1997; **40:** 271–5.
12. Kowalzick L, *et al.* Intralesional recombinant interferon beta-1a in the treatment of basal cell carcinoma: results of an open-label multicentre study. *Eur J Dermatol* 2002; **12:** 558–61.
13. Bostanci S, *et al.* Treatment of basal cell carcinoma located in the head and neck region with intralesional interferon alpha-2a: evaluation of long-term follow-up results. *Clin Drug Investig* 2005; **25:** 661–7.
14. Tucker SB, *et al.* Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006; **54:** 1033–8.
15. Granstein RD, *et al.* A controlled trial of intralesional recombinant interferon-γ in the treatment of keloidal scarring. *Arch Dermatol* 1990; **126:** 1295–1302.
16. Larrabee WF, *et al.* Intralesional interferon gamma treatment for keloids and hypertrophic scars. *Arch Otolaryngol Head Neck Surg* 1990; **116:** 1159–62.
17. Breitenstein S, *et al.* Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. *Br J Surg* 2009; **96:** 975–81.
18. Thirion P, *et al.* Alpha-interferon does not increase the efficacy of 5-fluorouracil in advanced colorectal cancer: Meta-analysis Group in Cancer. *Br J Cancer* 2001; **84:** 611–20.
19. Gill PS, *et al.* Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. *N Engl J Med* 1995; **332:** 1744–8.
20. Bukowski RM, *et al.* Treating cancer with PEG Intron: pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. *Cancer* 2002; **95:** 389–96.

Mycobacterial infections. For the use of interferon alfa in mycobacterial infections, see Interferon Gamma, p. 999.2.

Progressive multifocal leukoencephalopathy. Beneficial responses were reported in patients with HIV-associated progressive multifocal leukoencephalopathy (PML) after treatment with interferon alfa.[1] Daily intramuscular interferon alfa therapy for 2 weeks also resulted in some neurologic improvement in a patient identified as an asymptomatic human T-lymphotropic virus type I carrier, who developed PML and pneumocystis pneumonia.[2] However, in a retrospective analysis[3] of the relative value of HAART and interferon alfa in the treatment of PML associated with AIDS, prolonged survival associated with interferon alfa was found to be not independent of the effects of HAART and it was concluded that interferon alfa provided no additional benefit.

1. Huang SS, *et al.* Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol* 1998; **4:** 324–32.
2. Kimura A, *et al.* Progressive multifocal leukoencephalopathy in an HTLV-I carrier. *Clin Neurol Neurosurg* 2006; **108:** 768–71.
3. Geschwind MD, *et al.* The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol* 2001; **7:** 353–7.

Skin disorders. For the use of interferon alfa in skin disorders associated with raised IgE concentrations, see Interferon Gamma, p. 1000.1.

Warts. Various interferons have been tried by various routes in the treatment of anogenital warts (condylomata acuminata) (p. 1689.3).

Intralesional injection has been used to ensure relatively high concentrations of interferon in the wart but the occurrence of systemic adverse effects shows that there is absorption from this site. Complete responses were reported[1] in 36% of patients given intralesional interferon alfa-2b compared with 17% given placebo, and a corresponding overall reduction in the affected area of 62.4% compared with 1.2% respectively. However, follow-up was not sufficiently long to comment on relapse rates. Another study[2] found similar responses using interferons alfa-2b, alfa-n1, or beta in patients with refractory warts, with complete responses in 47% of patients given intralesional interferons compared with 22% of patients given placebo. A study[3] evaluating two different doses of intralesional interferon beta-1a given three times weekly for 3 weeks reported complete responses in 63% of lesions injected with 1 million units compared with 38% of lesions injected with 33 000 units. Good responses have also been reported in patients with both refractory and recurrent warts given intralesional interferon alfa-n3.[4] Relapses were delayed and fewer warts recurred in patients who had received interferon rather than placebo. Intralesional interferon alfa-2b used with podophyllum was more effective that podophyllum alone,[5] although about 66% of patients in each group subsequently relapsed. A systematic review concluded that based on limited available evidence intralesional interferons may have a therapeutic effect, but have no significant advantage over simpler and safer treatments.[6]

Topical application of interferon alfa has also been reported to be more effective than podophyllotoxin.[7,8] Interferon beta has also been applied topically after surgical removal of warts.[9]

Theoretically, *systemic* use should have advantages in controlling subclinical infections and reducing relapses. However, responses to subcutaneous interferon alfa have generally been disappointing[10-12] although responses comparable with cauterisation and a reduction in relapse rates with either subcutaneous or intramuscular interferon alfa-2b have been obtained.[13] Information on the use of systemic interferons as an adjunct to conventional therapy is scarce but a study in 97 patients[14] with recurrent warts found no difference in either response or relapse rates in patients given cryotherapy with subcutaneous interferon alfa or cryotherapy alone. A study comparing subcutaneous interferon alfa, beta, and gamma used with cryotherapy found no significant difference in response rate, although patients given interferon beta or gamma developed new warts at a lower frequency.[15]

Intralesional plus subcutaneous interferon alfa has also been tried in treatment of oral warts; 4 HIV-positive patients with recurrent oral warts that had failed to respond to surgery and other treatments responded to interferon alfa treatment.[16]

1. Eron LJ, *et al.* Interferon therapy for condylomata acuminata. *N Engl J Med* 1986; 315: 1059–64.
2. Reichman RC, *et al.* Treatment of condyloma acuminatum with three different interferons administered intralesionally: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 675–9.
3. Monsonego J, *et al.* Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. *Genitourin Med* 1996; **72:** 111–14.
4. Friedman-Kien AE, *et al.* Natural interferon alfa for treatment of condylomata acuminata. *JAMA* 1988; **259:** 533–8.
5. Douglas JM, *et al.* A randomized trial of combination therapy with intralesional interferon α_{2b} and podophyllin versus podophyllin alone for the therapy of anogenital warts. *J Infect Dis* 1990; **162:** 52–9.
6. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley: 2006 (accessed 13/06/08).
7. Syed TA, *et al.* Human leukocyte interferon-alpha versus podophyllotoxin in cream for the treatment of genital warts in males: a placebo-controlled, double-blind, comparative study. *Dermatology* 1995; **191:** 129–32.
8. Syed TA, *et al.* Management of genital warts in women with human leukocyte interferon-α vs podophyllotoxin in cream: a placebo-controlled, double-blind, comparative study. *J Mol Med* 1995; **73:** 255–8.
9. Gross G, *et al.* Recombinant interferon beta gel as an adjuvant in the treatment of recurrent genital warts: results of a placebo-controlled double-blind study in 120 patients. *Dermatology* 1998; **196:** 330–4.
10. Reichman RC, *et al.* Treatment of condyloma acuminatum with three different interferon-α preparations administered parenterally: a double-blind, placebo-controlled trial. *J Infect Dis* 1990; **162:** 1270–6.
11. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alfa-2a: a multicenter double-blind placebo-controlled clinical trial. *JAMA* 1991; **265:** 2684–7.
12. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alpha-2a: a multicenter double-blind placebo-controlled clinical trial. *Acta Derm Venereol (Stockh)* 1993; **73:** 223–6.
13. Panici PB, *et al.* Randomized clinical trial comparing systemic interferon with diathermocoagulation in primary multiple and widespread anogenital condyloma. *Obstet Gynecol* 1989; **74:** 393–7.
14. Eron LJ, *et al.* Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon. *Genitourin Med* 1993; **69:** 91–3.
15. Bonnez W, *et al.* A randomized, double-blind, placebo-controlled trial of systemically administered interferon-α, -β, or -γ in combination with cryotherapy for the treatment of condyloma acuminatum. *J Infect Dis* 1995; **171:** 1081–9.
16. Lozada-Nur F, *et al.* Use of intralesional interferon-alpha for the treatment of recalcitrant oral warts in patients with AIDS: a report of 4 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92:** 617–22.

Adverse Effects and Treatment

The adverse effects of interferon are varied and the natural products appear to be less toxic than the pure synthetic compounds. The frequency and severity of adverse effects of peginterferon alfa appear to be similar to those for interferon alfa although dose-related neutropenia and thrombocytopenia and injection site reactions are more common. Clinical experience suggests that interferons beta and gamma have similar adverse effects.

Adverse effects are generally mild and reversible at doses less than 5 million international units/day. The majority of patients on interferon treatment have 'flu-like' symptoms such as loss of appetite, fever, chills, fatigue, headache, malaise, myalgia, arthralgia, and sweating. These symptoms tend to be dose-related, are most likely to occur at the start of treatment, and mostly respond to paracetamol (but for a possible interaction with paracetamol, see Interactions, p. 995.2).

Other common adverse effects are alopecia, asthenia, weight loss, anxiety, depression, dermatitis, diarrhoea, irritability, nausea, nervousness, neutropenia, pruritus, sleep disturbances, taste alteration, and vomiting. Serious adverse effects reported include neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, and suicide) and neurological disturbances (confusion, coma, and seizures), severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anaemia), cardiovascular disorders (hypo- or hypertension, supraventricular arrhythmias and myocardial infarction), endocrine disorders (such as thyroid disorders and diabetes mellitus), pulmonary disorders (dyspnoea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic or ischaemic colitis), pancreatitis, and ophthalmologic disorders (such as decrease or loss of vision, retinopathy including macular oedema and retinal thrombosis or haemorrhages, optic neuritis and papilloedema).

Hypersensitivity reactions, including anaphylaxis, have occurred, and interferon therapy may cause or exacerbate auto-immune disorders (such as immune thrombocytopenia, thrombotic thrombocytopenic purpura, psoriasis, SLE, rheumatoid arthritis, and interstitial nephritis).

Hypertriglyceridaemia, sometimes severe, has been seen. High doses may cause electrolyte disturbances including decreased calcium concentrations. There may be signs of altered liver function and hepatitis has been reported. Renal failure and nephrotic syndrome have also occurred. Interferons may impair fertility and menstrual irregularities have been reported, particularly with interferon beta. Subcutaneous injection may produce a reaction at the injection site, mainly mild inflammation or erythema, but pain, hypersensitivity, and other non-specific reactions have been reported. The reaction is reported frequently with interferon beta, which can produce severe reactions including local necrosis.

Adverse effects of peginterferon alfa (alone or with ribavirin) reported in patients co-infected with hepatitis C virus and HIV, are similar to those reported in patients infected only with hepatitis C virus. Although haematological adverse effects such as neutropenia, thrombocytopenia, and anaemia occurred more often in co-infected patients, most patients could be managed by dose adjustments. Other adverse effects reported in co-infected patients given peginterferon and ribavirin include apathy, raised blood amylase, chapped lips, chromaturia, raised gamma-glutamyltransferase and hepatitis, influenza, lactic acidosis (including hyperlactacidaemia), lipodystrophy, mood alteration, pain in the pharynx, larynx, back, and limbs, pneumonia, and tinnitus. Peginterferon treatment was associated with decreases in CD4+ cell counts within the first 4 weeks that were reversible when the dose was reduced or stopped; no negative impact was noted on the control of HIV viraemia during treatment or follow-up.

Nasal dosage may produce mucosal irritation and damage.

Reviews.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Pardo M, *et al.* Risks and benefits of interferon-α in the treatment of hepatitis. *Drug Safety* 1995; **13:** 304–16.
3. Kirkwood JM, *et al.* Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002; **20:** 3703–18.
4. Sleijfer S, *et al.* Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; **27:** 423–31.
5. Rauschild A, *et al.* Practical guidelines for the management of interferon-α-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. *Cancer* 2008; **112:** 982–94.

Effects on the blood. Interferon alfa has myelosuppressive effects and the commonest haematological adverse effects associated with its use are dose-related leucopenia, neutropenia, and thrombocytopenia; anaemia is rarely reported. Other reported effects associated with interferon alfa include immune haemolytic anaemia[1] and immune thrombocytopenia.[2,3] Haemorrhage occurred in a patient with immune thrombocytopenia treated with interferon alfa,[4] and it was thought prudent to use interferons with caution, if at all, in this condition.[3,4] Reports of clotting disorders are rare; bleeding associated with induction of factor VIII inhibitor has been seen in a patient given interferon alfa to enhance hydroxycarbamide therapy for chronic myeloid leukaemia.[5] Thrombosis associated with interferon alfa has also been reported.[6]

Restoration of bone-marrow function after marrow transplantation was delayed in 3 patients given a human interferon alfa preparation.[7] Laboratory results showed an inhibition of granulocyte colony growth by human leucocyte interferon alfa. It was considered that interferon alfa was contra-indicated in patients with severe bone-marrow insufficiency and should not be given to marrow transplant patients before the graft was fully functional. However, in another 5 patients recombinant interferon alfa did not affect bone marrow transplants, although 3 patients had fever and chills, 4 had more than a 60% reduction in absolute peripheral granulocyte counts, and 4 had a 37 to 80% reduction in absolute platelet counts.[8] Lymphocytes were increased in all patients; blood counts returned to normal when interferon therapy stopped. Interferon alfa produced a decline in CD4+ T-lymphocytes resulting in opportunistic infections in 2 HIV-positive patients being treated for chronic hepatitis C.[9]

1. Akard LP, *et al.* Alpha-interferon and immune hemolytic anemia. *Ann Intern Med* 1986; **105:** 306.

2. McLaughlin P, *et al.* Immune thrombocytopenia following α-interferon therapy in patients with cancer. *JAMA* 1985; 254: 1353–4.
3. Färkkilä M, Iivanainen M. Thrombocytopenia and interferon. *BMJ* 1988; 296: 642.
4. Matthey F, *et al.* Bleeding in immune thrombocytopenic purpura after alpha-interferon. *Lancet* 1990; 335: 471–2.
5. English KE, *et al.* Acquired factor VIII inhibitor in a patient with chronic myelogenous leukaemia receiving interferon-alfa therapy. *Ann Pharmacother* 2000; 34: 737–9.
6. Durand JM, *et al.* Thrombosis and recombinant interferon-α. *Am J Med* 1993; 95: 115.
7. Nissen C, *et al.* Toxicity of human leucocyte interferon preparations in human bone-marrow cultures. *Lancet* 1977; i: 203–4.
8. Winston DJ, *et al.* Safety and tolerance of recombinant leukocyte A interferon in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1983; 23: 846–51.
9. Pesce A, *et al.* Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet* 1993; 341: 1597.

Effects on the cardiovascular system. Hypotension or hypertension, tachycardia, and distal cyanosis are the most commonly reported cardiovascular adverse effects. Other reported cardiac complications include cardiac arrhythmias, atrioventricular block, symptoms of ischaemic heart disease, including myocardial infarction and sudden death, congestive heart failure, acute dyspnoea, pericardial effusion,[1,2] and cardiomyopathy.[1,3,4] Cardiotoxicity was not related to the daily or cumulative total dose, or duration of treatment and is usually reversible on stopping interferon treatment.[1]

Peripheral vascular complications such as Raynaud's syndrome[5-9] have been associated with interferon alfa therapy and other types of interferon.

1. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest* 1991; 99: 557–61.
2. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; 10: 115–50.
3. Angulo MP, *et al.* Reversible cardiomyopathy secondary to α-interferon in an infant. *Pediatr Cardiol* 1999; 20: 293–4.
4. Kuwata A, *et al.* A case of reversible dilated cardiomyopathy after α-interferon therapy in a patient with renal cell carcinoma. *Am J Med Sci* 2002; 324: 331–4.
5. Bachmeyer C, *et al.* Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996; 135: 481–3.
6. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; 352: 878–9.
7. Kruit WH, *et al.* Interferon-α induced Raynaud's syndrome. *Ann Oncol* 2000; 11: 1501–2.
8. Schapira D, *et al.* Interferon-induced Raynaud's syndrome. *Semin Arthritis Rheum* 2002; 32: 157–62.
9. Iorio R, *et al.* Severe Raynaud's phenomenon with chronic hepatitis C disease treated with interferon. *Pediatr Infect Dis J* 2003; 22: 195–7.

Effects on the endocrine system. Both hypothyroidism and hyperthyroidism have been associated with interferon alfa therapy.[1] Thyroid disorders are usually minor and regress on stopping the interferon (with or without other specific treatment). However, patients with interferon alfa-induced Graves' disease may be less likely to remit once the drug is stopped.[1] Most such cases have occurred in patients being treated for hepatitis C,[1] and long-lasting ophthalmopathy has been reported in one patient.[2]

The development of type 1 diabetes has also been associated with interferon alfa therapy,[3-6] and exacerbation of existing type 2 diabetes has been reported.[7,8] Reversible hypopituitarism has been reported in patients receiving interferon alfa.[9,10] Recombinant interferon gamma was reported not to affect thyroid function.[11]

1. Tomer Y, *et al.* Interferon alpha treatment and thyroid dysfunction. *Endocrinol Metab Clin North Am* 2007; 36: 1051–66.
2. Binaghi M, *et al.* Ophtalmopathie de Basedow sévère liée à l'interféron alpha. *J Fr Ophtalmol* 2002; 25: 412–15.
3. Fabris P, *et al.* Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; 340: 548.
4. Guerci A-P, *et al.* Onset of insulin-dependent diabetes mellitus after interferon-alfa therapy for hairy cell leukaemia. *Lancet* 1994; 343: 1167–8.
5. Gori A, *et al.* Reversible diabetes in patient with AIDS-related Kaposi's sarcoma treated with interferon α-2a. *Lancet* 1995; 345: 1438–9.
6. Murakami M, *et al.* Diabetes mellitus and interferon-α therapy. *Ann Intern Med* 1995; 123: 318.
7. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; 313: 92.
8. Lopes EPA, *et al.* Exacerbation of type 2 diabetes mellitus during interferon-alfa therapy for chronic hepatitis B. *Lancet* 1994; 343: 244. Correction, *Ibid.*: 680.
9. Sakane N, *et al.* Reversible hypopituitarism after interferon-alfa therapy. *Lancet* 1995; 345: 1305.
10. Concha LB, *et al.* Interferon-induced hypopituitarism. *Am J Med* 2003; 114: 161–3.
11. Bhakri H, *et al.* Recombinant gamma interferon and autoimmune thyroid disease. *Lancet* 1985; ii: 457.

Effects on the eyes. The most typical ocular adverse effect associated with interferon alfa treatment is rednopathy, which is characterised by cotton wool spots and superficial retinal haemorrhages. Reports of interferon-associated retinopathy have been reviewed.[1,2] Reduced vision or complete visual loss is rare or limited and is usually reversible after stopping treatment. In a study of 43 patients with chronic hepatitis given interferon alfa, retinopathy developed in 11 of 37 non-diabetic patients and in 3 of 6 diabetic patients after about 8 to 10 weeks of therapy.[3] None of the patients had had retinopathy before treatment; the condition was reversible in the non-diabetic patients on stopping therapy. Visual acuity remained unchanged. Subconjunctival haemorrhage occurred in a further 3 of the non-diabetic patients. Severe irreversible loss of vision has been reported in a non-diabetic patient given interferon alfa.[4] A prospective study[5] of 156 patients treated with interferon alfa or peginterferon alfa (with or without ribavirin) reported signs of retinopathy in 24% of the patients; 29 patients developed cotton-wool spots, 7 developed retinal haemorrhage, and 2 patients developed both lesions during treatment; none of the patients had retinopathy before starting treatment. The lesions remained asymptomatic and resolved in all the patients. Patient age above 45 years, hypertension, and the use of pegylated alpha-interferon were identified as risk factors for retinopathy. Neurovisual impairment was present in 31 patients before interferon treatment and in 74 patients during treatment. Another study[6] of 19 patients reported that 8 patients developed asymptomatic retinopathy while on treatment with interferon alfa (with or without ribavirin); patients who had previously failed to respond to interferon monotherapy seemed more likely to develop retinopathy when given combined therapy than patients who had responded and then relapsed. The changes were transient and sometimes disappeared while the patients were still on treatment. Retinopathy has occasionally been reported in patients being treated with interferon beta for the management of multiple sclerosis.[7-9] Symptoms also resolved after stopping treatment.

Pain in one eyeball leading to exophthalmos and complete visual loss has been reported in a patient given interferon alfa;[10] despite withdrawal of interferon and instigation of antibacterial and corticosteroid treatment, the eyeball subsequently ruptured necessitating ophthalmectomy. Other severe ocular effects reported during interferon alfa treatment include a disorder resembling Vogt-Koyanagi-Harada disease, central retinal vein occlusion, central retinal artery occlusion, and bilateral ischaemic optic neuropathy with severe visual impairment.[11]

Interferon-alfa is not usually known to cause ocular surface toxicity, however, epithelial microcyst formation has been reported in a patient after using topical interferon alfa-2b for 4 weeks.[12]

1. Hayasaka S, *et al.* Interferon associated retinopathy. *Br J Ophthalmol* 1998; 82: 323–5.
2. Savant V, Gillow T. Interferon-associated retinopathy. *Eye* 2003; 17: 534–6.
3. Hayasaka S, *et al.* Retinopathy and subconjunctival haemorrhage in patients with chronic viral hepatitis receiving interferon alfa. *Br J Ophthalmol* 1995; 79: 150–2.
4. Lohmann CP, *et al.* Severe loss of vision during adjuvant interferon alfa-2b treatment for malignant melanoma. *Lancet* 1999; 353: 1326.
5. d'Alteroche L, *et al.* Ophthalmologic side effects during alpha-interferon therapy for viral hepatitis. *J Hepatol* 2006; 44: 56–61.
6. Jain K, *et al.* Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001; 85: 1171–3.
7. Saito H, *et al.* Retinopathy in a multiple sclerosis patient undergoing interferon-therapy. *Multiple Sclerosis* 2007; 13: 939–40.
8. Longmuir R, *et al.* Cotton wool spots associated with interferon beta-1 alpha therapy. *Semin Ophthalmol* 2007; 22: 49–53.
9. Polden DV, *et al.* Interferon beta-associated retinopathy in patients treated for multiple sclerosis. *Neurology* 2008; 70: 1153–5.
10. Yamada H, *et al.* Acute onset of ocular complications with interferon. *Lancet* 1994; 343: 914.
11. Sène D, *et al.* Intraocular complications of IFN-alpha and ribavirin therapy in patients with chronic viral hepatitis C. *World J Gastroenterol* 2007; 13: 3137–40.
12. Aldave AJ, Nguyen A. Ocular surface toxicity associated with topical interferon alpha-2b. *Br J Ophthalmol* 2007; 91: 1087–8.

Effects on the gastrointestinal tract. Mild and transient gastrointestinal adverse effects such as nausea, diarrhoea, vomiting, and anorexia occur in about 30 to 40% of patients being treated with interferon alfa. There have been reports[1-4] of the onset of coeliac disease during treatment of hepatitis C with interferon or peginterferon alfa, in some cases used with ribavirin. Symptoms generally resolved after interferon was stopped and a gluten-free diet started. A case[5] of eosinophilic enteritis has been reported in a patient, with no history of digestive disorders, after 12 weeks of recombinant interferon alfa-2b treatment; symptoms resolved after stopping interferon and on treatment with prednisolone. New[6,7] or exacerbated[8] cases of ulcerative colitis have been reported in patients on interferon or peginterferon alfa treatment (with or without ribavirin). Treatment with interferon was usually stopped[7,8] and symptoms tended to resolve or improve with appropriate therapy (such as mesalazine and/or corticosteroids).[6-8] Cases of ischaemic colitis associated with interferon or peginterferon alpha have been reported rarely.[9]

1. Bardella MT, *et al.* Celiac disease during interferon treatment. *Ann Intern Med* 1999; 131: 157–8.
2. Cammarota G, *et al.* Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *Lancet* 2000; 356: 1494–5.
3. Bourlière M, *et al.* Onset of coeliac disease and interferon treatment. *Lancet* 2001; 357: 803–4.
4. Martins EV, Gaburri AK. Celiac disease onset after pegylated interferon and ribavirin treatment of chronic hepatitis C. *Arq Gastroenterol* 2004; 41: 132–3.
5. Kakumitsu S, *et al.* Eosinophilic enteritis observed during alpha-interferon therapy for chronic hepatitis C. *J Gastroenterol* 2000; 35: 548–51.
6. Mavrogiannis C, *et al.* Ulcerative colitis associated with interferon treatment for chronic hepatitis C. *J Hepatol* 2001; 34: 964–5.
7. Sprenger R, *et al.* Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis. *Gut* 2005; 54: 438–9.
8. Watanabe T, *et al.* A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon alpha-2b and ribavirin. *Gut* 2006; 55: 1682–3.
9. Leung Y, *et al.* Ischemic colitis during pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Can J Gastroenterol* 2006; 20: 661–3.

Effects on the hair. Excessive temporary loss of telogen hair causing moderate and reversible alopecia occurs in about 7 to 30% of patients on interferon or peginterferon alfa treatment. Alopecia areata[1-3] and alopecia universalis[4,5] have occasionally been reported; complete regrowth of the hair usually occurs on completing interferon treatment. Alopecia has also been reported after use of topical interferon alfa eye drops for 3 months.[6]

A report of marked greying of the hair in a patient beginning after 5 months of treatment with interferon alfa for metastatic malignant melanoma; on completion of interferon therapy the hair regrowth returned to its normal colour.[7] Marked straightening of scalp and body hair has been reported in 2 patients after combined treatment with interferon alfa-2b or peginterferon alfa-2b and ribavirin for chronic hepatitis C.[8] In the first patient, there was also diffuse thinning of scalp hair, change in hair texture, increased greying of the hair, and eyebrow lengthening; the original curly hair began to regrow 6 months after stopping treatment, but the hair abnormalities recurred on rechallenge despite switching from interferon alfa-2b to peginterferon alfa-2b. In the second patient, treatment with peginterferon alfa-2b and ribavirin was associated with straightening of scalp hair, eyebrow hair, and pubic hair.[8] Lengthening and thickening of eyelashes has also been reported with interferon alfa therapy.[9,10] A case of eyelid and eyebrow trichomegaly has also been reported[11] in a patient treated with peginterferon alfa and ribavirin.

1. Radny P, *et al.* Alopecia areata induced by adjuvant treatment with alpha-interferon in malignant melanoma? *Dermatology* 2004; 209: 249–50.
2. Agesta N, *et al.* Alopecia areata during interferon alpha-2b/ribavirin therapy. *Dermatology* 2002; 205: 300–1.
3. Kemland KH, Hunziker T. Alopecia areata induced by interferon alpha? *Dermatology* 1999; 198: 418–19.
4. Tallani G, *et al.* Reversible alopecia universalis during treatment with PEG-interferon and ribavirin for chronic hepatitis C. *J Chemother* 2005; 17: 212–14.
5. Kartal ED, *et al.* Reversible alopecia universalis secondary to PEG-interferon alpha-2b and ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Eur J Gastroenterol Hepatol* 2007; 19: 817–20.
6. Finger PT, Reichstein D. Interferon alpha eye drops: treatment of atypical lymphoid hyperplasia with secondary alopecia. *Br J Ophthalmol* 2007; 91: 1085–6.
7. Fleming CJ, MacKie RM. Alpha interferon-induced hair discolouration. *Br J Dermatol* 1996; 135: 337–8.
8. Bessis D, *et al.* Straight hair associated with interferon-alfa plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002; 147: 392–3.
9. Hernández-Núñez A, *et al.* Trichomegaly following treatment with interferon alpha-2b. *Lancet* 2002; 359: 1107.
10. Dikici B, *et al.* Interferon alpha and hypertrichosis of eyelashes. *Pediatr Infect Dis J* 2002; 21: 448–9.
11. Bowaiti M. Pegylated interferon-induced eyelid and eyebrow trichomegaly during chronic hepatitis C. *J Gastroenterol Hepatol* 2005; 20: 1945–6.

Effects on hearing. Sensorineural hearing loss, mostly unilateral, has been rarely reported in patients treated with interferon or peginterferon. A prospective study[1] reported sensorineural hearing loss in 18 of 49 patients and tinnitus in 14 of 49 patients given interferons. The authors reported that effects were more common in those given interferon beta than in those given interferon alfa, and resolved in all patients on stopping therapy. A report[2] of 6 patients who had sudden hearing loss while on treatment with peginterferon alfa plus ribavirin found that hearing loss did not fully resolve after stopping treatment; but neither did it worsen in those who continued their treatment. A case report[3] of a patient who had acute sensorineural hearing loss 2 months after starting treatment with peginterferon alfa and ribavirin found that when treatment was re-started 4 months after stopping, the patient did not have further hearing loss and hearing on the left-side was unaffected. In another case report[4] a patient who developed hearing loss 22 weeks after starting treatment with peginterferon alfa, continued with treatment and symptoms did not worsen. Hearing loss resolved within 2 weeks of stopping treatment.

1. Kanda Y, *et al.* Sudden hearing loss associated with interferon. *Lancet* 1994; 343: 1134–5.
2. Formann E, *et al.* Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin. *Am J Gastroenterol* 2004; 99: 873–7.
3. Wong VK, *et al.* Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. *World J Gastroenterol* 2005; 11: 5392–3.
4. Ellouni H, *et al.* Sudden hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment. *World J Gastroenterol* 2007; 13: 5411–12.

Effects on the kidneys. Renal adverse effects associated with interferon alfa are usually limited to mild, asymptomatic proteinuria and moderate increases in serum creat-

inine in 15 to 20% of patients. Dose-related asymptomatic proteinuria has been reported with interferon gamma treatment.[1] Acute renal failure and nephrotic syndrome associated with interferon alfa treatment is rare and has mostly been reported in patients with underlying renal disease, or malignancies,[2-5] and in those receiving high doses.[6] Cases have also been reported in patients receiving interferon or peginterferon alfa treatment for chronic hepatitis C.[7-9] Nephrotic syndrome has also occurred after use of interferon beta.[10-12] Renal dysfunction usually resolves after stopping treatment, but incomplete resolution and fatalities have been reported.[5,8]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; 10: 115–50.
2. Averbuch SD, *et al.* Acute interstitial nephritis with the nephrotic syndrome following recombinant leukocyte A interferon therapy for mycosis fungoides. *N Engl J Med* 1984; 310: 32–5.
3. Selby P, *et al.* Nephrotic syndrome during treatment with interferon. *BMJ* 1985; 290: 1180.
4. Herrman J, Gabriel F. Membranoproliferative glomerulonephritis in a patient with hairy-cell leukemia treated with alpha-II interferon. *N Engl J Med* 1987; 316: 112–13.
5. Colovic M, *et al.* Interferon alpha sensitisation induced fatal renal insufficiency in a patient with chronic myeloid leukaemia: case report and review of literature. *J Clin Pathol* 2006; 59: 879–81.
6. Kramer P, *et al.* Recombinant leucocyte interferon A induces steroid-resistant acute vascular rejection episodes in renal transplant recipients. *Lancet* 1984; i: 989–90.
7. Endo M, *et al.* Appearance of nephrotic syndrome following interferon-α therapy in a patient with hepatitis B virus and hepatitis C virus coinfection. *Am J Nephrol* 1998; 18: 439–43.
8. Fisher ME, *et al.* A woman with chronic hepatitis C infection and nephrotic syndrome who developed multiple renal lesions after interferon alfa therapy. *Am J Kidney Dis* 2004; 44: 567–73.
9. Couto CA, *et al.* Life-threatening thrombocytopenia and nephrotic syndrome due to focal segmental glomerulosclerosis associated with pegylated interferon alpha-2b and ribavirin treatment for hepatitis C. *Liver Int* 2006; 26: 1294–7.
10. Nakao K, *et al.* Minimal change nephrotic syndrome developing during postoperative interferon-beta therapy for malignant melanoma. *Nephron* 2002; 90: 498–500.
11. Auty A, Saleh A. Nephrotic syndrome in a multiple sclerosis patient treated with interferon beta 1a. *Can J Neurol Sci* 2005; 32: 366–8.
12. Kumasaka R, *et al.* Nephrotic syndrome associated with interferon-beta-1b therapy for multiple sclerosis. *Clin Exp Nephrol* 2006; 10: 222–5.

Effects on lipids. Cases[1-3] of reversible hypertriglyceridaemia (with or without elevation of total cholesterol level) have been reported with interferon alfa treatment. Hypertriglyceridaemia more often occurs with longer treatment durations and does not appear to be related to pre-existing cardiovascular disorders or baseline dyslipidaemia; frequency and severity are not dose dependent. Lifestyle modifications and drug treatment with a fibrate or statin are usually needed to reduce triglyceride levels. A small study[4] reported that taking omega-3 fatty acid supplements (3 g daily for 6 months) reduced serum triglyceride levels in patients on interferon alfa for the management of chronic hepatitis C.

1. Graessle D, *et al.* Alpha-interferon and reversible hypertriglyceridemia. *Ann Intern Med* 1993; 118: 316–17.
2. Junghans V, Rünger TM. Hypertriglyceridaemia following adjuvant interferon-α treatment in two patients with malignant melanoma. *Br J Dermatol* 1999; 140: 183–4.
3. Wong SF, *et al.* Management of hypertriglyceridemia in patients receiving interferon for malignant melanoma. *Ann Pharmacother* 2004; 38: 1635–9.
4. Malaguarnera M, *et al.* Fish oil treatment of interferon-alpha-induced dyslipidaemia: study in patients with chronic hepatitis C. *BioDrugs* 1999; 11: 285–91.

Effects on the liver. Mild hepatotoxicity with an asymptomatic and reversible rise in serum aminotransferases has been reported in about 25 to 30% of patients receiving interferon alfa; severe hepatotoxicity is rare[1] but cases of fatal liver failure have been reported,[2-5] sometimes due to severe exacerbation of chronic hepatitis B and/or C infection.[4,5] An analysis of the toxicity of adjuvant high-dose interferon alfa in 40 patients being treated for melanoma reported hepatotoxicity in 39 patients, with 26 patients having grade 3 to 4 hepatotoxicity.[6] Cases[7,8] of peginterferon alfa-induced auto-immune hepatitis have been reported in patients receiving treatment for chronic hepatitis C.

Raised serum-alanine aminotransferase values have been reported in about 37% of patients given interferon beta therapy for the treatment of multiple sclerosis, with grade 3 to 4 hepatotoxicity being reported in about 1.4% of patients.[9]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; 10: 115–50.
2. Durand JM, *et al.* Liver failure due to recombinant alpha interferon. *Lancet* 1991; 338: 1268–9.
3. Wandl UB, *et al.* Liver failure due to recombinant alpha interferon for chronic myelogenous leukaemia. *Lancet* 1992; 339: 123–4.
4. Marcellin P, *et al.* Fatal exacerbation of chronic hepatitis B induced by recombinant alpha-interferon. *Lancet* 1991; 338: 828.
5. Janssen HLA, *et al.* Fatal hepatic decompensation associated with interferon alfa. *BMJ* 1993; 306: 107–8.
6. Jonasch E, *et al.* Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma. *Cancer J* 2000; 6: 139–45.
7. Kogure T, *et al.* Fulminant hepatic failure in a case of autoimmune hepatitis in hepatitis C during peg-interferon-alpha 2b plus ribavirin treatment. *World J Gastroenterol* 2007; 13: 4394–7.
8. Kontorinis N, *et al.* Pegylated interferon-induced immune-mediated hepatitis post-liver transplantation. *Liver Transpl* 2006; 12: 827–30.
9. Bymes V, *et al.* Drug induced liver injury secondary to interferon-beta (IFN-beta) in multiple sclerosis. *Ann Hepatol* 2006; 5: 56–9.

Effects on the nervous system and mental state. Neurological adverse effects have been reported with interferon alfa treatment for chronic hepatitis C virus or for malignant diseases;[1-3] notably, an acute confusional state may develop rapidly after starting high-dose interferon alfa treatment and a depressive syndrome may develop more slowly over weeks to months of treatment. Less commonly a manic condition, usually characterised by extreme irritability and agitation but also occasionally by euphoria, may occur.

Acute interferon alfa-induced confusional states are typically characterised by disorientation, lethargy, difficulties with speaking and writing, parkinsonism, psychomotor retardation, psychotic symptoms (such as hallucinations), and somnolence.

Depression[5-9] occurs in about 16 to 58% of patients receiving interferon alfa. Patients considered to be at risk for developing depression are those with pre-existing symptoms of mood and anxiety disorders, those with a history of major depression, and those receiving higher doses of interferon alfa or on long treatment regimens. SSRIs have been used successfully to both treat patients with interferon-associated depression, thus allowing therapy to be continued,[10,11] and as pretreatment to prevent its occurrence.[12]

Should manic symptoms[13] occur, interferon alfa and antidepressant treatment should be stopped and a mood stabiliser given. Interferon alfa-induced mood disorders may also consist of an overlap between depressive and manic symptoms. A prospective study[14] of 93 patients treated with peginterferon alfa plus ribavirin for chronic hepatitis C reported that mood disorders occurred in 30 patients; 3 cases of mania, 15 cases of irritable hypomania, and 12 cases of mixed depressive states. The distinction between the 2 states is important in terms of management as depression-specific symptoms respond well to SSRIs, whereas antidepressants may worsen manic or hypomanic states.

Seizures[15-17] attributed to interferon alfa have been described.

Cases of neurological toxicity have been reported in patients receiving interferon beta,[1,18] although interferon beta is considered to be slightly less neurotoxic.

Chronic hepatitis C virus infection may be complicated by the development of systemic vasculitis caused by mixed cryoglobulinemia or of a non-cryoglobulinemic vasculitis resembling polyarteritis nodosa. Successful treatment of the hepatitis infection with interferon alfa usually results in the improvement of vasculitic symptoms, including neuropathy. However, vasculitis may also be precipitated or exacerbated by treatment with interferon (including peginterferon alfa)[19-22] resulting in development of vasculitic neuropathy. Non-vasculitic peripheral neuropathies, including cranial neuropathies; have also been reported.[20-23] Others[24] have reported no association between peginterferon alfa and peripheral neuropathy. In most cases symptoms improved on treatment with cortcosteroids or spontaneously, but fatal exacerbations of vasculitis have occurred despite stopping the interferon treatment and giving immunosuppressants.[21]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; 10: 115–50.
2. Dieperink E, *et al.* Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. *Am J Psychiatry* 2000; 157: 867–76.
3. Malek-Ahmadi P. Mood disorders associated with interferon treatment: theoretical and practical considerations. *Ann Pharmacother* 2001; 35: 489–95.
4. Van Gool AR, *et al.* Neuropsychiatric side effects of interferon-alfa therapy. *Pharm World Sci* 2003; 25: 11–20.
5. Raison CL, *et al.* Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs* 2005; 19: 105–23.
6. Janssen HLA, *et al.* Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994; 21: 241–3.
7. Renault PF, *et al.* Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987; 147: 1577–80.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Depression with interferon. *Aust Adverse Drug React Bull* 1999; 18: 6.
9. Capuron L, Ravaud A. Prediction of the depressive effects of interferon alfa therapy by the patient's initial affective state. *N Engl J Med* 1999; 340: 1370.
10. Levenson JL, Fallon BJ. Fluoxetine treatment of depression caused by interferon-α. *Am J Gastroenterol* 1993; 88: 760–1.
11. Schramm TM, *et al.* Sertraline treatment of interferon-alfa-induced depressive disorder. *Med J Aust* 2000; 173: 359–61.
12. Musselman DL, *et al.* Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001; 344: 961–6.
13. Kingsley D. Interferon-alpha induced 'tertiary mania'. *Hosp Med* 1999; 60: 381–2.
14. Constant A, *et al.* Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry* 2005; 66: 1050–7.
15. Janssen HLA, *et al.* Seizures associated with low-dose α-interferon. *Lancet* 1990; 336: 1580.
16. Brouwers PJ, *et al.* Photosensitive seizures associated with interferon alpha-2a. *Ann Pharmacother* 1999; 33: 113–14.
17. Ameen M, Russell-Jones R. Seizures associated with interferon-α treatment of cutaneous malignancies. *Br J Dermatol* 1999; 141: 386–7.
18. Goeb JL, *et al.* Psychiatric side effects of interferon-beta in multiple sclerosis. *Eur Psychiatry* 2006; 21: 186–93.
19. Batisse D, *et al.* Sustained exacerbation of cryoglobulinaemia-related vasculitis following treatment of hepatitis C with peginterferon alfa. *Eur J Gastroenterol Hepatol* 2004; 16: 701–3.
20. Boonyapisit K, Katirji B. Severe exacerbation of hepatitis C-associated vasculitic neuropathy following treatment with interferon alpha: a case report and literature review. *Muscle Nerve* 2002; 25: 909–13.
21. Beuthien W, *et al.* Vasculitic complications of interferon-alpha treatment for chronic hepatitis C virus infection: case report and review of the literature. *Clin Rheumatol* 2005; 24: 507–15.
22. Stübgen JP. Interferon alpha and neuromuscular disorders. *J Neuroimmunol* 2009; 207: 3–17.
23. Gastineau DA, *et al.* Severe neuropathy associated with low-dose recombinant interferon-alpha. *Am J Med* 1989; 87: 116.
24. Briani C, *et al.* Peripheral neurotoxicity of pegylated interferon alpha: a prospective study in patients with HCV. *Neurology* 2006; 67: 781–5.

Effects on the oral mucosa. Painful oral ulcers, necessitating withdrawal of interferon alfa therapy, have occurred in a patient treated for chronic hepatitis.[1] Interferon alfa treatment has been reported to exacerbate pre-existing lichen planus associated with chronic hepatitis C.[2,3] New cases of oral lichen planus have been reported in patients receiving interferon alfa treatment for malignant disease[4] and chronic hepatitis.[5]

1. Qaseem T, *et al.* A case report of painful oral ulcerations associated with the use of alpha interferon in a patient with chronic hepatitis due to non-A non-B non-C virus. *Mil Med* 1993; 158: 126–7.
2. Arelas J, *et al.* Lichen planus and chronic hepatitis C: exacerbation of the lichen under interferon-alpha-2a therapy. *Eur J Gastroenterol Hepatol* 1996; 8: 825–8.
3. Nagao Y, *et al.* Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C. *Int J Mol Med* 2005; 15: 237–41.
4. Kütting B, *et al.* Oropharyngeal lichen planus associated with interferon-α treatment for mycosis fungoides: a rare side-effect in the therapy of cutaneous lymphomas. *Br J Dermatol* 1997; 137: 836–7.
5. Guijarro Guijarro B, *et al.* Aparición de un liquen plano erosivo durante el tratamiento con interferón alfa-2a por una hepatitis C crónica. *Med Oral* 2001; 6: 358–63.

Effects on the respiratory system. Pulmonary adverse effects have occasionally been reported with interferon or peginterferon alfa treatment. A literature review[1] found that the most commonly reported adverse effect was interstitial pneumonitis, followed by a sarcoid-like reaction with non-caseating granuloma formation. Other, less commonly reported events were asthma exacerbation, pleural effusion, bronchiolitis obliterans with organizing pneumonia, and a case of fatal acute respiratory distress-like syndrome (ARDS). A subsequent case of ARDS associated with peginterferon alfa therapy has also been reported.[2]

1. Midturi J, *et al.* Spectrum of pulmonary toxicity associated with the use of interferon therapy for hepatitis C: case report and review of the literature. *Clin Infect Dis* 2004; 39: 1724–9.
2. Vartany E, *et al.* Adult respiratory distress syndrome after treatment with pegylated interferon α-2a and ribavirin. *Heart Lung* 2008; 37: 153–6.

Effects on skeletal muscle. Myalgia is one of the 'flu-like' symptoms frequently associated with interferons. Rhabdomyolysis[1-3] has occurred in patients being treated with interferon alfa and proved fatal when associated with multiple organ failure in a patient receiving adjuvant high-dose interferon alfa for multiple myeloma.[1] Rhabdomyolysis has also been reported in a patient receiving interferon beta for the treatment of multiple sclerosis.[4] Other rarely reported muscular disorders associated with interferon alfa therapy include inflammatory myopathies, polymyositis-like symptoms, and a case of mitochondrial myopathy.[5]

1. Reinhold U, *et al.* Fatal rhabdomyolysis and multiple organ failure associated with adjuvant high-dose interferon alfa in malignant melanoma. *Lancet* 1997; 349: 540–1.
2. Gabrielli M, *et al.* Acute reversible rhabdomyolysis during interferon alpha2b therapy for hepatitis C. *Am J Gastroenterol* 2003; 98: 940.
3. Ozdag F, *et al.* Acute rhabdomyolysis during the treatment of sclerœmyxedema with interferon alfa. *J Dermatolog Treat* 2001; 12: 167–9.
4. Lünemann JD, *et al.* Rhabdomyolysis during interferon-beta 1a treatment. *J Neurol Neurosurg Psychiatry* 2002; 72: 274. Correction *ibid.*; 73: 354.
5. Stübgen JP. Interferon alpha and neuromuscular disorders. *J Neuroimmunol* 2009; 207: 3–17.

Effects on the skin. Dermatological adverse effects such as dryness, erythema, rash, or urticaria, have been reported in about 5 to 12% of patients given interferon alfa; severe events occur rarely.[1] Exacerbation or development of psoriasis was reported in patients given recombinant interferon alfa[2-4] peginterferon alfa,[5] and interferon beta-1a.[6] However, no such effect was seen in 7 patients given interferon gamma.[7] Both vitiligo and psoriasis developed in a 10 year-old girl with chronic hepatitis B infection given interferon alfa; the skin conditions did not improve on stopping the interferon treatment.[8] A case[9] of vitiligo occurring during the third month of treatment for chronic hepatitis C with peginterferon alfa and ribavirin has been reported the condition persisted after treatment with peginterferon was completed. Exacerbation of lichen planus has also been reported[10] during interferon alfa treatment (see also Effects on the Oral Mucosa, above). Cases of cutaneous sarcoidosis have been reported in patients with chronic hepatitis C being treated with interferon or pegylated interferon alfa plus ribavirin; skin lesions are usually benign and treatment with interferon alfa may sometimes be continued with resolution of the skin lesions occurring

spontaneously or within a few months of completing treatment.[11,12] Cutaneous vascular lesions with punctate telangiectasias were noted in 18 of 44 patients treated with interferon alfa-2a; lesions did not appear at the injection site.[13] Severe necrotising cutaneous lesions were reported at injection sites in a patient given recombinant interferon beta-1b; the lesions healed when interferon alfa-n3 was substituted.[14] However, cutaneous necrosis has also been associated with interferon alfa[15,16] and peginterferon alfa.[17] Five cases[18] of a self-resolving cutaneous lesion at the injection site of interferon, mimicking lupus erythematosus, have been reported; 3 of them involved interferon alfa therapy for malignant melanoma and the other 2 patients were being given interferon beta for multiple sclerosis. Fatal paraneoplastic pemphigus developed in a patient given interferon alfa-2a.[19] Hyperpigmentation of the skin and tongue has been described[20] in 2 dark-skinned patients during treatment with interferon alfa and ribavirin.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; 10: 115–50.
2. Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet* 1986; i: 1466–8.
3. Funk J, *et al.* Psoriasis induced by interferon-α. *Br J Dermatol* 1991; 125: 463–5.
4. Taylor C, *et al.* Extensive psoriasis induced by interferon alfa treatment for chronic hepatitis C. *Postgrad Med J* 2000; 76: 365–6.
5. Ketikoglou I, *et al.* Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol* 2005; 15: 107–9.
6. López-Lerma I, *et al.* New-onset psoriasis in a patient treated with interferon beta-1a. *Br J Dermatol* 2009; 160: 716–7.
7. Schulze H-J, Mahrle G. Gamma interferon and psoriasis. *Lancet* 1986; ii: 926–7.
8. Seçkin D, *et al.* Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. *Pediatr Dermatol* 2004; 21: 577–9.
9. Tomasiewicz K, *et al.* Vitiligo associated with pegylated interferon and ribavirin treatment of patients with chronic hepatitis C: a case report. *Adv Therapy* 2006; 23: 139–42.
10. Protzer U, *et al.* Exacerbation of lichen planus during interferon alfa-2a therapy for chronic active hepatitis C. *Gastroenterology* 1993; 104: 903–5.
11. Eberlein-König B, *et al.* Cutaneous sarcoid foreign body granulomas developing in sites of previous skin injury after systemic interferon-alpha treatment for chronic hepatitis C. *Br J Dermatol* 1999; 140: 370–2.
12. Hurst EA, Mauro T. Sarcoidosis associated with pegylated interferon alfa and ribavirin treatment for chronic hepatitis C: a case report and review of the literature. *Arch Dermatol* 2005; 141: 865–8.
13. Dreno B, *et al.* Alpha-interferon therapy and cutaneous vascular lesions. *Ann Intern Med* 1989; 111: 95–6.
14. Sheremata WA, *et al.* Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. *N Engl J Med* 1995; 332: 1584.
15. Shinohara K. More on interferon-induced cutaneous necrosis. *N Engl J Med* 1995; 333: 1222.
16. Sasseville D, *et al.* Interferon-induced cutaneous necrosis. *J Cutan Med Surg* 1999; 3: 320–3.
17. Bessis D, *et al.* Necrotizing cutaneous lesions complicating treatment with pegylated-interferon alfa in an HIV-infected patient. *Eur J Dermatol* 2002; 12: 99–102.
18. Arrue I, *et al.* Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol* 2007; 34 (suppl 1): 18–21.
19. Kirsner RS, *et al.* Treatment with alpha interferon associated with the development of paraneoplastic pemphigus. *Br J Dermatol* 1995; 132: 474–8.
20. Willems M, *et al.* Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; 149: 390–4.

Shock. Fatal non-cardiogenic shock occurred after the third dose of interferon alfa-2b in a patient with malignant melanoma.[1] There were similarities to a fatal reaction reported in another patient with malignant melanoma (see under Effects on Skeletal Muscle, p. 994.3).

1. Carson JJ, *et al.* Fatality and interferon α for malignant melanoma. *Lancet* 1998; 352: 1443–4.

Precautions

Interferons should be used with caution or avoided altogether in patients with depression or psychiatric disorders, epilepsy or other CNS diseases, severe renal or hepatic impairment, chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver, auto-immune hepatitis, cardiac disorders, myelosuppression, poorly controlled thyroid dysfunction, pulmonary disease, diabetes mellitus, auto-immune diseases, coagulation disorders, or a history of these conditions.

All patients receiving interferons should be closely monitored for any signs or symptoms of psychiatric disorders; if psychiatric symptoms continue or worsen, or suicidal ideation is identified, then interferon therapy should be stopped.

Interferon treatment is not advised for patients whose hypoglycaemia, hyperglycaemia and/or diabetes mellitus is not effectively controlled; if these conditions develop during treatment and cannot be controlled with medication then interferon treatment should be stopped. Standard blood and biochemical laboratory tests (including thyroid function) should be done before starting treatment with interferon and then periodically during therapy. Interferon should be used with caution in patients also receiving other potentially myelosuppressive agents.

Assessment of cardiac function is advised before treatment is started in patients with pre-existing cardiac abnormalities and if there is any deterioration of cardiovascular status interferon should be suspended or stopped.

Hepatic and renal function should be monitored during treatment with interferons. Interferon treatment should be stopped in patients who develop evidence of liver decompensation during treatment. Treatment should also be stopped in those patients who despite the dose of interferon being reduced still have progressive and clinically significant increases in serum-alanine aminotransferase.

Patients receiving interferons who have visual disturbances should undergo eye examination. A baseline ocular examination is recommended before treatment, and periodic eye examinations should be performed throughout treatment in patients predisposed to retinopathy, such as those with diabetes mellitus or hypertension; treatment should be stopped in patients who develop new or worsening ophthalmologic disorders.

Patients with psoriasis or sarcoidosis have been reported to have exacerbations during interferon alfa therapy.

Patients should receive adequate fluids to maintain hydration during treatment with interferon alfa since hypotension related to fluid depletion has been seen in some patients.

Interferons may affect the ability to drive or operate machinery.

Antibodies may develop to exogenous interferon that reduce its activity.

Asthma. For a report of severe exacerbation of asthma in patients receiving interferon alfa, see Effects on the Respiratory System, p. 994.3.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of interferon alfa by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. It has been suggested that interferons are too large in molecular weight to transfer into breast milk in clinically relevant amounts.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 12/06/08)
2. Kumar AR, *et al.* Transfer of interferon alfa into human breast milk. *J Hum Lact* 2000; 16: 226–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies interferon alfa-2a and peginterferon alfa-2a as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed. Interferon alfa-2b and peginterferon alfa-2b are classified as possibly porphyrinogenic; they should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Psychiatric disorders. For comment on the risk of mood disorders in patients with a history of such disorders, see Effects on the Nervous System and Mental State, p. 994.2.

Interactions

Interactions involving interferons have not been fully evaluated, but it is known that they can inhibit hepatic oxidative metabolism via cytochrome P450 enzymes; the clinical relevance of this interaction is unclear and thus caution should be exercised during use with drugs metabolised in this way. Studies with peginterferon alfa showed increased activity of the cytochrome P450 isoenzymes CYP2C8/9 and CYP2D6; caution is advised when giving peginterferon alfa with drugs that are metabolised by these isoenzymes, such as warfarin, phenytoin, and flecainide. Interferon and peginterferon alfa have been shown to inhibit the metabolism of theophylline which is metabolised via the cytochrome P450 isoenzyme CYP1A2. Drugs likely to exacerbate the haematological effects of interferons, such as ribavirin and zidovudine, should also be used with caution. Interferons may also increase the neurotoxic and cardiotoxic effects of other drugs.

ACE inhibitors. For a report of possible synergistic haematological toxicity in patients receiving interferon alfa and ACE inhibitors, see p. 1288.3.

Analgesics. Three patients had increases in liver enzyme values when given *paracetamol* 1 g two or three times daily on the same three days each week as interferon alfa; vinblastine was also given every third week.[1] Paracetamol has also been found to enhance the antiviral effect of interferon alfa in healthy subjects.[2]

1. Kellokumpu-Lehtinen P, *et al.* Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; i: 1143.
2. Hendrix CW, *et al.* Modulation of α-interferon's antiviral and clinical effects by aspirin, acetaminophen, and prednisone in healthy volunteers. *Antiviral Res* 1995; 28: 121–31.

Anticoagulants. For reference to potentiation of *acenocoumarol* or *warfarin* necessitating dosage reduction in patients also receiving interferon alfa, see p. 1533.1.

Antineoplastics. For reduction in the area under the plasma concentration-time curve for *melphalan* in patients receiving interferon alfa, see p. 820.3.

Antivirals. For a report of synergistic bone-marrow toxicity with interferon alfa and *zidovudine*, see p. 1026.3.

Thalidomide. For reports of toxicity associated with interferons and thalidomide, see p. 870.3.

Theophylline. For reference to reduced clearance of theophylline in patients receiving interferon alfa, see p. 1235.2.

Antiviral Action

Interferons are naturally occurring proteins produced by eukaryotic cells in response to viral infection and other biological inducers that confer protection on uninfected cells of the same species. They are cytokines that affect many cell functions and have, in addition to their antiviral activity, antiproliferative and immunoregulatory properties. Three major classes have been identified: alfa, beta and gamma. Interferon alfa and beta are classified as Type I interferons and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities; interferon gamma in particular is a potent macrophage-stimulating factor.

Interferons exert their biological effect by binding to specific receptors on the surface of human cells. After binding, a cascade of intracellular events, including the induction of certain enzymes, occurs. This process is thought to be responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Pegylated interferons have similar, but possibly slightly weaker, actions to the native forms.

Studies have shown interferons to have benefit in infections with hepatitis B virus, hepatitis C virus, herpes simplex viruses, varicella-zoster virus, CMV, rhinoviruses, and papillomaviruses.

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. More than 80% of a subcutaneous or intramuscular dose of interferon alfa is absorbed. After intramuscular injection, interferon alfa produced by recombinant techniques and that from cultured leucocytes produce similar plasma concentrations although there is a large interindividual variation. Plasma concentrations are dose-related; and peak concentrations usually occur within 4 to 8 hours, returning to baseline by 16 to 24 hours. After intravenous doses, serum interferon levels decline at a slightly faster rate than after subcutaneous or intramuscular use and are undetectable 4 hours after infusion. After systemic use low levels of interferon are detected in respiratory secretions, CSF, eye, and brain. The elimination half-life of interferon alfa is about 2 to 7 hours after subcutaneous or intramuscular injections and 2 hours after intravenous infusion. Interferon alfa undergoes renal catabolism and negligible amounts of interferons are excreted in the urine; biliary excretion and liver metabolism are minor pathways of elimination.

The attachment of interferon to large inert macrogol (polyethylene glycol; PEG) molecules, termed pegylation, substantially reduces the rate of absorption and excretion of interferon and increases the plasma concentration. After a subcutaneous dose of peginterferon alfa-2b the maximum serum concentration occurs in about 15 to 44 hours and high concentrations are sustained for 48 to 72 hours; the mean elimination half-life is about 40 hours. The maximum serum concentration of peginterferon alfa-2a occurs about 72 to 96 hours after subcutaneous dosing and the mean terminal half-life is approximately 160 hours. The absolute bioavailability of peginterferon alfa-2a is 84% and is similar to that of unmodified interferon alfa-2a.

Reviews.

1. Zeuzem S, *et al.* Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003; 23 (suppl 1): 23–8.

2. Pedder SC. Pegylation of interferon alfa: structural and pharmacokinetic properties. *Semin Liver Dis* 2003; 23 (suppl 1): 19–22.
3. Caliceti P. Pharmacokinetics of pegylated interferons: what is misleading? *Dig Liver Dis* 2004; 36 (suppl 3): S334–9.
4. Bressler B, *et al.* Pharmacokinetics and response of obese patients with chronic hepatitis C treated with different doses of PEG-IFN alpha-2a (40KD) (PEGASYS). *Br J Clin Pharmacol* 2009; 67: 280–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avirostat; Bioferon; INF; Infostat; Inter 2-B; Intron A Peg; Pegasys; *Austral.*: Intron A; Pegasys; PegIntron; Roferon-A; *Austria*: IntronA; Pegasys; PegIntron; Roferon-A; *Belg.*: IntronA; Pegasys; PegIntron; Roferon-A; *Braz.*: Beferon†; Blauferon; Intron A; Kinnoferon 2A; Pegasys; PegIntron; Roferon-A; *Canad.*: Infergen†; Intron A; Pegasys; Unitron PEG†; *Chile*: Intermax-Alpha†; IntronA; Pegasys; PegIntron; Roferon-A; *China*: An Da Fen (安达芬); An Fu Long (安福隆); An Te Fu (安特芙); Bei Er Fen (贝尔芬); Chang Sheng De Jia (长生德佳); Chang Sheng Fu Kang (长生扶康); Chang Sheng Fu Ming (长生扶明); Di En An (迪恩安); Di Ning (滴宁); Fu Li Sheng (复力生); Hapgen (运德素); Infergen (干复津); Intefen (因特芬); Interlong (英特龙); Intron A (甘乐能); Jie Fu (捷抚); Kaifu (凯孚); Lai Fu Long (莱福隆); Li Fen Neng (利分能); Li Ya Mei (里亚美); Longhuanuo (隆化诺); Opin (奥平); Pegasys (派罗欣); PegIntron (佩乐能); Roferon-A (罗菲恒); Sai Ruo Jin (赛若金); Shu Run (淑润); Shuangyinjie (爽因洁); Wan Fu Luo (万复洛); Wan Fu Yin (万复因); Xin Fu Ning (辛复宁); Xin Hua Nuo (辛化诺); Yi Sheng (益生); YiLin (忆林); You Jing An (尤靖安); You Ni Long (尤尼隆); Yuan Ce Su (远策素); *Cz.*: Alfaferone†; IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; Viraferon†; ViraferonPeg; *Denm.*: IntronA; Multiferon; Pegasys; PegIntron; *Fin.*: IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; *Fr.*: IntronA; Pegasys; Roferon-A; ViraferonPeg; *Ger.*: IntronA; Pegasys; PegIntron; Roferon-A; *Gr.*: Advaferon; Inferax; Infergen; IntronA; Pegasys; PegIntron; Roferon-A; *Hong Kong*: Intron A; Pegasys; PegIntron; Roferon-A†; *Hung.*: Egiferon; Intron A; Pegasys; PegIntron; Roferon-A; *India*: Alferon; Intalfa; Intron A; Intron A; LG Intermax Alpha; Roferon-A; *Indon.*: Interferon Alfanative†; IntronA; Kalferon; Pegasys; PegIntron; *Irl.*: IntronA; Pegasys; PegIntron; Roferon-A; ViraferonPeg; *Israel*: Intron A; Pegasys; PegIntron; Roferon-A; *Ital.*: Alfaferone; IntronA; Pegasys; PegIntron; Roferon-A; *Jpn*: Canferon†; OIF; Pegasys; PegIntron; Roferon-A†; Sumiferon; *Malaysia*: Intron A; Pegasys; PegIntron; Roferon-A; *Mex.*: Alferon; FNI 2B†; Heberon Alfa; Intron A; Lemeron†; Nisoftat†; Pegasys; Pegtron; Proquiferon; Roferon-A†; Urifron; *Neth.*: IntronA; Pegasys; PegIntron; Roferon-A; ViraferonPeg; *Norw.*: IntronA; Multiferon; Pegasys; PegIntron; Roceron; *NZ*: Intron A; Pegasys; PegIntron; Roferon-A; *Philipp.*: Intron A; Pegasys; PegIntron; Roferon-A; Shanferon; Uniferon; *Pol.*: Alfaferone; Intron A; Pegasys; PegIntron; Roferon-A; ViraferonPeg; *Port.*: Intron A; Pegasys; PegIntron; Roferon-A; Viraferon†; ViraferonPeg; *Rus.*: Alfaferone (Альфаферон); Alfarona (Альфарона); Altevir (Альтевир); Infagel (Инфагель); Inferon (Инферон); Interal (Интераль); Intron A (Интрон А); Leucinferon (Лейкинферон); Lifferon (Лайфферон); Locferon (Локферон); Pegasys (Пегасис); PegIntron (Пегинтрон); Reaferon Lipint (Реаферон Липинт); Realdiron (Реальдирон); Roferon-A (Роферон-А); Viferon (Виферон); Wellferon (Вэллферон)†; *S.Afr.*: Intron A; Multiferon†; Pegasys; PegIntron; Roferon-A; *Singapore*: Intron A; Pegasys; PegIntron; Roferon-A; *Spain*: Intron A; Pegasys; PegIntron; Roferon-A; *Swed.*: IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; *Switz.*: Cylatron; Intron A; Pegasys; PegIntron; Roferon-A; *Thai.*: Bioferon; INF†; Intron A; Pegasys; PegIntron; *Turk.*: Intron A; Pegasys; PegIntron; Roferon-A; *UK*: IntronA; Pegasys; PegIntron; Roferon-A; ViraferonPeg; *Ukr.*: Alfiron (Альфирон); Alpharekin (Альфарекин); Genferon (Генферон); Intron A (Интрон-а); Laferobion (Лаферобион); Laferon (Лаферон); Lipoferon (Липоферон); Nazoferon (Назоферон); Ophthalmoferon (Офтальмоферон); Pegasys (Пегасис); PegIntron (Пегинтрон); Realdiron (Реальдирон); Roferon-A (Роферон-А); Viferon (Виферон); Virogel (Вирогель); *USA*: Alferon N†; Infergen; Intron A; Pegasys; PegIntron; Sylatron; *Venez.*: Intron A; Intron; Pegasys; PegIntron; Roferon-A.

Multi-ingredient Preparations. *Arg.*: Bioferon Hepakit; *Austral.*: Pegasys RBV; Pegatron; Rebetron†; *Canad.*: Pegasys RBV; Pegetron; *Hong Kong*: Rebetron†; *Mex.*: Hepatron C†; Pegtron Cotronak Kit; *NZ*: Pegasys RBV; Pegatron; Rebetron†; Roferon-A RBV; *Philipp.*: Pegasys RBV; *Rus.*: Genferon (Генферон); Genferon Light (Генферон Лайт); Herpferon (Герпферон); Hyaferone (Гиаферон); Kipferon (Кипферон); Ophtalmoferon (Офтальмоферон); *Ukr.*: Herpferon (Герпферон)†.

Pharmacopoeial Preparations

BP 2014: Interferon Alfa-2a Injection.

Interferon Beta *(BAN, rINN)*

IFN-β; Interferón-β; Interferon-β; Interferón beta; Interféron Bêta; Interferoni beta; Interferonum Beta; SH-Y-579A (interferon beta-1b); Интерферон Бета.

CAS — 74899-71-1 (interferon beta); 145258-61-3 (interferon beta-1a); 145155-23-3 (interferon beta-1b); 90598-63-3 (interferon beta-1b).

ATC — L03AB02 (natural); L03AB07 (1a); L03AB08 (1b).

ATC Vet — QL03AB02 (natural); QL03AB07 (1a); QL03AB08 (1b).

UNII — XRO4566Q4R (interferon beta-1a); TTD90R31WZ (interferon beta-1b).

NOTE. Interferon beta was previously known as fibroblast interferon.

Interferon beta-1a and Interferon beta-1b are both *USAN.*

Pharmacopoeias. *Eur.* (see p. vii) includes Interferon Beta-1a Concentrated Solution.

Ph. Eur. 8: (Interferon Beta-1a Concentrated Solution). A solution of a glycosylated protein having the same amino acid sequence and disulphide bridge and a similar glycosylation pattern as interferon beta produced by human diploid fibroblasts in response to viral infections and various other inducers. It is produced by a method based on recombinant DNA technology, using mammalian cells in culture. It contains a minimum 0.20 mg of protein per mL, and has a minimum potency of $1.5X10^8$ units per mg of protein. It may contain buffer salts. A clear or slightly opalescent, colourless or slightly yellowish liquid. Store in airtight containers at a temperature below -70 degrees. Protect from light.

Nomenclature. Interferon beta may be derived from fibroblasts, or produced by recombinant DNA technology. Subspecies of the human beta gene produce interferon beta with protein variants designated by a number (as in interferon beta-1). Interferon beta-1 is further qualified by a letter to indicate the amino-acid sequences at positions 1 and 17, and to indicate whether or not glycosylation is present:

- interferon beta-1a has methionine at position 1 and cysteine at 17 and is glycosylated at position 80
- interferon beta-1b has serine at position 17 and is not glycosylated

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rch) indicates production from genetically engineered Chinese hamster ovary cells; (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology.

Uses and Administration

Interferon beta is a cytokine with antiviral and immunomodulating activities. Two forms of interferon beta are available: interferon beta-1a and interferon beta-1b (see Nomenclature, above). Interferon beta is mainly used in the management of relapsing-remitting multiple sclerosis (below), although its mode of action is unclear; pegylated interferon beta-1a is also being investigated. In the UK interferon beta-1b is also licensed for use in secondary progressive multiple sclerosis.

Interferon beta-1a is given in relapsing-remitting multiple sclerosis in a dose dependent upon the formulation used:

- *Avonex* (*Biogen*) is given in a dose of 6 million units (30 micrograms) once weekly by intramuscular injection.
- *Rebif* (*Serono*) is given in an escalating dose over 4 weeks, to 12 million units (44 micrograms) three times weekly by subcutaneous injection, or to 6 million units (22 micrograms) three times weekly by subcutaneous injection in patients unable to tolerate the higher dose.

Interferon beta-1b is given in both relapsing-remitting and in secondary progressive multiple sclerosis in an escalating dose over 3 to 6 weeks to a dose of 8 million units (250 micrograms) on alternate days by subcutaneous injection.

In the UK interferon beta-1a and interferon beta-1b are also indicated for the treatment of patients who have had a single demyelinating event with an active inflammatory process if it is sufficiently severe to warrant intravenous corticosteroids.

Reviews.

1. Goodkin DE. Interferon beta-1b. *Lancet* 1994; 344: 1057–60.
2. Etheridge LJ, *et al.* The use of interferon beta in relapsing-remitting multiple sclerosis. *Arch Dis Child* 2004; 89: 789–91.
3. Markowitz CE. Interferon-beta: mechanism of action and dosing issues. *Neurology* 2007; 68 (suppl 4): S8–S11.
4. Bertolotto A, Gilli F. Interferon-beta responders and non-responders: a biological approach. *Neurol Sci* 2008; 29 (suppl 2): S216–S217.
5. Demina TL, *et al.* Efficacy and safety of prolonged immunomodulatory treatment with interferon beta. *Neurosci Behav Physiol* 2009; 39: 497–9.
6. Smith D. Interferon-beta therapy for multiple sclerosis—is the injection site the relevant action site? *J Neuroimmunol* 2009; 215: 117–21.
7. Sanford M, Lyseng-Williamson KA. Subcutaneous recombinant interferon-β-1a (Rebif): a review of its use in the treatment of relapsing multiple sclerosis. *Drugs* 2011; 71: 1865–91.

Guillain-Barré syndrome. Rapid improvement in motor function was reported during use of interferon beta-1a in a patient with Guillain-Barré syndrome associated with *Campylobacter jejuni* infection.[1] However, the relative contributions of interferon therapy and a course of plasma exchange that immediately preceded it could not be assessed.[2] Successful treatment of Guillain-Barré syndrome was reported in a patient after interferon beta-1a was added to treatment with intravenous immunoglobulin.[3] A small randomised, placebo-controlled pilot study[4] of subcutaneous interferon beta-1a or placebo, in addition to intravenous immunoglobulin, in patients with Guillain-Barré syndrome reported no significant difference in the rate of improvement.

1. Créange A, *et al.* Treatment of Guillain-Barré syndrome with interferon-β. *Lancet* 1998; 352: 368.
2. Sawaya RA. Interferon beta for Guillain-Barré syndrome. *Lancet* 1998; 352: 1550–1.
3. Schaller B, *et al.* Successful treatment of Guillain-Barré syndrom : with combined administration of interferon-β-1a and intravenous immunoglobulin. *Eur Neurol* 2001; 46: 167–8.
4. Pritchard J, *et al.* A randomized controlled trial of recombinant interferon-beta 1a in Guillain-Barré syndrome. *Neurology* 2001; 61: 1282–4.

Multiple sclerosis. Multiple sclerosis (MS)[1-4] is a chronic inflammatory and demyelinating disease affecting the CNS. It is the most common disabling neurological disease among young adults and is most often diagnosed in those between the ages of 20 and 40, with women being almost twice as likely to develop it as men. Although the etiology and pathogenesis of MS is poorly understood, it is thought that the disease has an immunological basis and occurs in genetically susceptible individuals. MS is characterised by multiple areas of inflammation and demyelination; activated T-cells enter the CNS and produce an immune cascade resulting in localised loss of myelin, oligodendrocytes, and axons. The resulting lesions (plaques) accumulate over time, with impairment or less electrical transmission along the nerve fibres (axons).

Patients with MS commonly present with an individual mix of **symptoms**, which tend to progress over years to decades. The type and number of symptoms may vary according to the areas affected but typically include bowel and bladder dysfunction, changes in cognitive function, dizziness, depression, fatigue, difficulties with walking and balance, paraesthesias, pain, sexual dysfunction, spasticity, problems with speech and swallowing, tremor, and visual impairment, notably from optic neuritis. Most patients improve to some degree after the initial attack but the course and severity of the disease are unpredictable.

People with MS generally follow one of four clinical **courses** of disease, which in turn may be mild, moderate, or severe. In about 85% of patients the disease follows a *relapsing-remitting course (RR-MS)* in which there are recurrent exacerbations (flare-ups) followed by clinical improvement and relatively long periods of remission. After about 10 to 15 years up to 50% of patients develop progressive neurological deterioration, categorised as *secondary progressive disease (SP-MS).* However, about 15% of people with RR-MS will have a mild course with little or no disability after 15 years *(benign MS).* About 10 to 15% of patients present without relapses but have slow continuous deterioration, classified as *primary progressive disease (PP MS).* In about 5% of patients the disease is described as *progressive relapsing*; people with this type of MS have steadily worsening disease from the onset but also have acute exacerbations.

Choice of treatment.

Drugs with immunological actions (disease-modifying drugs) have been tried in the treatment of MS itself with the aim of improving recovery from acute attacks, preventing or reducing further attacks (relapses), and halting the progression of the underlying pathology.[5] Different therapies are used for patients having acute attacks for patients who have RR-MS, for patients who have the progressive subtypes, and for symptomatic management. Combination therapies are also being investigated, particularly in patients who have failed treatment with a single immunomodulatory agent.

Corticosteroids are used for their immunomodulatory and anti-inflammatory effects in acute attacks (relapses). Corticosteroid therapy reduces the duration of the episode and accelerates recovery, but it is unknown whether it alters the course of the disease in the long term.[6] The drug of choice is methylprednisolone; usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days and sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g daily have been tried.[7] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis,[8] although the effect was not sustained beyond 2 years.[9] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[10] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[11] A small clinical study indicated that the bioavailability attained after large doses of oral prednisone may be similar to that of high dose intravenous methylprednisolone.[12] In patients with PP MS, the benefits of short-course methylprednisolone lasted no longer than 3 months[13] although, in patients with SP-MS, a preliminary study has suggested that progression may be

delayed by intermittent high-dose methylprednisolone therapy.[14]

Interferon beta has become established for treatment of RR-MS in selected patients, and is also used in SP-MS. Studies[15-17] in patients with active RR-MS have shown the efficacy of interferon *beta-1b* given subcutaneously and at different doses. Similar results in RR-MS have been obtained with interferon *beta-1a* given by either subcutaneous or intramuscular routes;[18-20] although comparative studies[21,22] have suggested that subcutaneous interferon beta-1a (44 micrograms given three times a week) is more effective than intramuscular interferon beta-1a (30 micrograms weekly). A prospective, randomised, multicentre study[23] comparing the different frequencies of dosing with interferon beta-1a and beta-1b concluded that high-dose interferon beta-1b given on alternate days was more effective in RR-MS than once-weekly interferon beta-1a. Studies[24-26] in patients presenting with a first demyelinating event (clinically isolated syndrome), or other manifestation of early disease, have shown that treatment with interferon beta may reduce the rate of progression to clinical MS, a view confirmed by a recent systematic review.[27] A 3-year follow-up analysis[28] of one study[26] found that early treatment with interferon beta-1b prevented the development of confirmed disability.

Concern has been expressed over the detection of neutralising antibodies against interferon in up to 46% of patients;[29-31] development of neutralising antibodies correlates with reduced treatment efficacy and the possibility for renewed disease activity. The development of neutralising antibodies is greater in patients treated with higher doses of interferon and in those treated with interferon beta-1b.[32] Recommendations have been made on using antibody titres to guide treatment.[33]

Some encouraging results have also been obtained with interferon beta in patients with SP-MS.[34] However, no effect has been found on disability progression from use of interferon beta (-1a or -1b) in SP-MS[35,36] or PP-MS.[37]

Results of studies[38,39] with *glatiramer* in patients with RR-MS have shown that it can reduce the number of relapses and may produce some improvements in neurological disability. Follow-up of these patients for about 3 years continued to show a beneficial effect on disease relapse rate. MRI data supported the beneficial clinical results.[40,41] When compared, interferon beta-1b and glatiramer acetate had similar clinical efficacy and led to similar suppression of disease activity as shown on monthly brain MRI in patients with RR-MS.[41] These benefits are produced in different ways leading to expectations of possible treatment with both drugs. Early treatment with glatiramer has also been shown to be effective in delaying conversion to clinical multiple sclerosis in patients presenting with clinically isolated syndrome and MRI-detected brain lesions.[42]

Natalizumab is a humanised monoclonal antibody that has been found to decrease the frequency of exacerbations in RR-MS. A 2-year randomised, placebo-controlled study[43] to assess the safety and efficacy of intravenous natalizumab reported a 68% likelihood of remaining relapse-free and a 83% reduction in the number of new or enlarging brain lesions on MRI; the cumulative probability of sustained disability progression was 17% in the natalizumab patient group compared with 29% in the placebo group. Another 2-year study[44] reported that natalizumab plus intramuscular interferon beta-1a was more effective than interferon beta-1a monotherapy. Patients receiving combination therapy were 55% less likely to relapse and had a 83% reduction in the number of new or enlarging brain lesions on MRI compared with monotherapy. A 23% probability of progression of disability was reported for the combination treatment group compared with 29% for interferon alone. Although the combination of natalizumab and glatiramer acetate is considered to be potentially antagonistic, a phase II, randomised, double-blind, placebo-controlled study found that natalizumab added to existing glatiramer acetate therapy, in patients with RR-MS who had had at least one relapse, was well tolerated and showed no apparent loss in efficacy during the 6-month study period.[45] Natalizumab has, however, been associated with an increased risk of progressive multifocal leukoencephalopathy and its use is therefore limited to patients with highly active RR-MS who have had an inadequate response to, or are unable to tolerate, other therapies.

Although some studies have shown modest benefits with *immunosuppressants*, the general conclusions of large controlled studies have tended to be that any slight benefits of existing therapies with immunosuppressants such as azathioprine, ciclosporin, cyclophosphamide, and methotrexate are outweighed by the toxicity of the doses required to have an effect.[46-53] However, a systematic review[54] concluded that azathioprine reduced the number of patients who had relapses and the number who progressed during the first 2 to 3 years of treatment. It considered that azathioprine might be given as an alternative to interferon beta for maintenance treatment for patients who frequently relapse and require corticosteroids. Long-term toxicity (including the risk of malignancy) may be related to cumulative doses above 600 g and treatment for longer than 10 years. Mitoxantrone (given by intravenous infusion) has been studied in patients with RR-, PR-, and SP-MS and found to be moderately effective in reducing disease progression and the frequency of relapses.[55,56] Its use may, however, be limited by dose-related cardiotoxicity and the risk of therapy-related acute leukaemia;[57] it is suggested that mitoxantrone be used to treat patients with rapidly progressive disease or those not responding to high-dose interferon. While most current recognised treatments are only available for parenteral use, fingolimod[58-60] is an oral immunomodulator used to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate, which binds to sphingosine 1-phosphate receptors blocking the emergence of lymphocytes from the lymph nodes thereby reducing the number of lymphocytes into peripheral blood. It is presumed that this reduces the migration of lymphocytes into the CNS. Fingolimod has been shown to reduce relapse rates and improve MRI outcomes in RR-MS compared with intramuscular interferon beta.[60] Teriflunomide is an oral pyrimidine synthesis inhibitor with immunomodulatory effects. It has reduced relapse rates, reduced the risk of disability progression (at the higher dose of 14 mg daily), and improved MRI measures of disease activity in patients with RR-MS.[61] Clinical studies have been carried out with other oral drugs including the immunosuppressants cladribine[62,63] and laquinimod.[64,65] A review[62] of cladribine indicated that it reduced the number of enhancing lesions but also had significantly more adverse effects (including myelosuppression) than placebo. The authors suggested that cladribine might have a role in the treatment of refractory patients with SP-MS. In the randomised, placebo-controlled, multicentre CLARITY study,[63] treatment with oral cladribine significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity at 96 weeks in patients with RR-MS. An increased incidence of lymphocytopenia and herpes zoster was also noted. A phase II placebo-controlled study[64] determined that oral laquinimod (300 micrograms) daily was effective in suppressing development of active lesions in RR-MS and a later study[65] reported that a daily dose of 600 micrograms laquinimod significantly reduced MRI-measured disease activity.

Other immunological approaches evaluated have included the use of monoclonal antibodies such as alemtuzumab, daclizumab, and rituximab, and immunosuppressants such as mycophenolate mofetil. Although alemtuzumab was found to be more effective than interferon beta-1a in patients with early RR-MS, the study had to be stopped early due to 6 cases of immune thrombocytopenic purpura, including one death, in those receiving alemtuzumab.[66] HMG-CoA reductase inhibitors (statins) have immunomodulatory effects and a small study[67] reported that simvastatin significantly decreases the number and volume of new MRI lesions in patients with RR-MS. An open label study in a few patients with RR-MS and breakthrough disease found that adding doxycycline to their current treatment with interferon beta-1a was safe and effective.[68] Dimethyl fumarate is thought to have immunomodulatory and neuroprotective effects, partly through activation of cellular defence against oxidative stress. In placebo-controlled studies[69,70] it has reduced relapse rates and improved some other outcome measures in RR-MS.

A systematic review[71] on the use of intermittent intravenous normal immunoglobulins in patients with RR-MS concluded that there was a reduction in relapse rate and an increased time to relapse, but no evidence that immunoglobulin treatment reduces the progression of MS or reverses existing damage. Intravenous normal immunoglobulins are not effective in SP-MS.[72] Autologous haematopoietic stem cell transplantation has shown benefit in some patients with progressive MS.[73,74]

Guidelines for the management of multiple sclerosis have been produced in the UK,[75,76] the USA,[77] and other countries.[78,79]

Symptomatic treatment.

MS can produce a wide range of symptoms, many of which are manageable; symptomatic treatment is aimed at the management of spasticity, ataxia, tremor, paroxysmal symptoms, pain, fatigue, and bladder dysfunction. Baclofen, dantrolene, diazepam, and tizanidine are the usual drugs given for spasticity (see p. 2014.2). Nabiximols (a mixture of cannabis extracts containing dronabinol and cannabidiol) is used as adjunctive treatment for spasticity and neuropathic pain in multiple sclerosis. While there is some anecdotal evidence to suggest that cannabis and individual cannabinoids, including synthetic cannabinoids such as nabilone, may improve pain and spasticity,[80] a review[81] considered evidence of efficacy to be lacking. Patients with MS can suffer from different types of pain, including pain from spasticity, and therapy must be individualised for each specific pain syndrome (see Choice of Analgesic, p. 4.2). Pain, spasms, and spasticity have responded to gabapentin in preliminary studies.[82-87] A review has noted, however, that the absolute and comparative efficacy and tolerability of anti-spasticity drugs is poorly documented.[88] Paraesthesia and dysaesthesia, which can be common, may respond to tricyclic antidepressants or antiepileptics. Amantadine, modafinil, pemoline, and fampridine have all been investigated for the management of fatigue associated with MS.[89] Treatment of bladder dysfunction may include an alpha blocker such as phenoxybenzamine and appropriate parasympathomimetic or antimuscarinic (such as oxybutynin) therapy to control bladder contractions (see Urinary Incontinence and Retention, p. 2349.2). Fampridine and amifampridine have been reported to produce beneficial symptomatic responses such as improvement in walking, dexterity, and vision, possibly as a result of potassium-channel blocking activity but an early systematic review[90] was unable to come to a conclusion about safety and efficacy, noting that publication bias posed a problem. However, subsequent to positive findings in further multicentre randomised controlled studies, fampridine is licensed for use in patients with MS who have difficulty walking.

Conventional treatments are only partially effective and may produce adverse effects, and many patients with MS try alternative therapies. The most common *dietary interventions* are supplementation with polyunsaturated fatty acids (such as omega-3 and omega-6 fatty acids, often as fish, evening primrose, or sunflower oils), allergen-free diets, vitamins, and micronutrients and antoxidants (such as selenium, ginkgo biloba extracts, and coenzyme Q10). A review of the relationship between these dietary interventions and MS concluded that there was insufficient evidence to determine their benefits or risks.[91] Polyunsaturated fatty acids seem to have no major effect on disease progression and recurrence of exacerbations over 2 years. Research into the value of vitamin D is ongoing after findings that higher levels of serum vitamin D are associated with a lower risk of MS.[92]

The use of *hyperbaric oxygen* therapy in MS was a matter of debate for many years. Some workers reported benefit, especially in bladder and bowel function or in cerebellar function whereas others were unable to substantiate any long-term benefit and reviews have concluded that there is no convincing evidence that hyperbaric oxygen therapy is useful.[93,94]

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The symbol † denotes a preparation no longer actively marketed

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Rheumatoid arthritis. Preliminary studies suggested that interferon beta might have a beneficial effect on rheumatoid arthritis,[1] the conventional management of which is described on p. 13.2. However, a subsequent randomised, double-blind study[2] found that adding subcutaneous interferon beta to methotrexate treatment in patients with rheumatoid arthritis had no clinical or radiological benefit over adding placebo.

1. van Holten J, *et al.* Interferon-β for treatment of rheumatoid arthritis? *Arthritis Res* 2002; 4: 346–52.
2. van Holten J, *et al.* A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 64–9.

Warts. For the use of interferon beta in the management of warts, see Interferon Alfa, p. 992.1.

Adverse Effects

As for interferons in general (see Interferon Alfa, p. 992.2).

Severe local reactions at injection sites, including tissue necrosis, have been reported. Menstrual irregularities have been associated with interferon beta use. On injection, transient neurological symptoms that may mimic an exacerbation of multiple sclerosis have been reported. In addition transient episodes of hypertonia and/or severe muscular weakness may occur at any time during treatment.

Reviews.
1. Bayas A, Rieckmann P. Managing the adverse effects of interferon-beta therapy in multiple sclerosis. *Drug Safety* 2000; 22: 149–59.

Auto-immune disorders. Reversible subacute cutaneous lupus erythematosus[1] and SLE[2] have been reported in patients given interferon beta. A case[3] of lupus erythematosus profundus has been reported in a patient after 4 years of treatment with interferon beta-1b for multiple sclerosis; the neurological symptoms and subcutaneous nodules resolved after stopping treatment. There have been case reports of patients developing myasthenia gravis while receiving interferon beta; the patients responded to treatment with pyridostigmine.[4]

1. Nousari HC, *et al.* Subacute cutaneous lupus erythematosus associated with interferon beta-1a. *Lancet* 1998; 352: 1825–6.
2. Crispín JC, Díaz-Jouanen E. Systemic lupus erythematosus induced by therapy with interferon-β in a patient with multiple sclerosis. *Lupus* 2005; 14: 495–6.
3. Gono T, *et al.* Lupus erythematosus profundus (lupus panniculitis) induced by interferon-β in a multiple sclerosis patient. *J Clin Neurosci* 2007; 14: 997–1000.
4. Dionisiotis J, *et al.* Development of myasthenia gravis in two patients with multiple sclerosis following interferon β treatment. *J Neurol Neurosurg Psychiatry* 2004; 75: 1079.

Effects on the blood. Aplastic anaemia occurred[1] in a patient with multiple sclerosis after treatment with interferon beta-1a for about a year. The interferon was stopped and the patient had a good response to immunosuppressant treatment. The haematological effects of subcutaneous interferon beta-1a in multiple sclerosis patients have been reviewed.[2]

1. Aslam AK, Singh T. Aplastic anemia associated with interferon beta-1a. *Am J Ther* 2002; 9: 522–3.
2. Rieckmann P, *et al.* Haematological effects of interferon-beta-1a (Rebif) therapy in multiple sclerosis. *Drug Safety* 2004; 27: 745–56.

Effects on the cardiovascular system. Severe Raynaud's syndrome developed in a patient during treatment with interferon beta.[1] Symptoms subsided once interferon beta was stopped.

1. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; 352: 878–9.

Effects on the eyes. Interferon beta does not typically cause retinopathy but some cases have been reported see Interferon Alfa, p. 993.1.

Effects on hearing. For a report of sensorineural hearing loss in patients receiving interferon beta, see Interferon Alfa, p. 993.3.

Effects on the liver. Hepatotoxicity, sometimes severe and in rare cases fatal, has been reported with interferons and its association specifically with the use of interferon beta-1a in multiple sclerosis patients has been reviewed.[1]

1. Francis GS, *et al.* Hepatic reactions during treatment of multiple sclerosis with interferon-β-1a: incidence and clinical significance. *Drug Safety* 2003; 26: 815–27.

Effects on the skin. Calcified subcutaneous nodules have been reported in a patient after 3 years of treatment with subcutaneous interferon beta-1a for the treatment of multiple sclerosis.[1] For reports of severe necrotising cutaneous lesions at injection sites, and the development of psoriasis, in patients receiving interferon beta, see Interferon Alfa, p. 994.3. See also Auto-immune Disorders, above for a report of cutaneous lupus erythematosus associated with interferon beta.

1. Macbeth AE, *et al.* Calcified subcutaneous nodules: a long-term complication of interferon beta-1a therapy. *Br J Dermatol* 2007 157: 624–5.

Precautions

As for interferons in general (see Interferon Alfa, p. 993.1).

Interferon beta in high doses is fetotoxic and abortifacient in *primates* and should be avoided during pregnancy.

Antibody formation. For comment on the formation of neutralising antibodies to interferon beta, and their influence on its efficacy, see Multiple Sclerosis under Uses, p. 996.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies interferon beta-1a and -1b as probably not porphyrinogenic; they may be

used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for interferons in general (see Interferon Alfa, p. 995.2).

Antiviral Action

As for interferons in general (see Interferon Alfa, p. 995.3).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. About 50% of a subcutaneous dose and 40% of an intramuscular dose of interferon beta is absorbed. For some formulations of interferon beta-1a, bioavailability and area under the plasma concentration-time curves are equivalent for subcutaneous and intramuscular dosage, but for others, intramuscular doses produce higher values than subcutaneous doses and subcutaneous doses therefore cannot be substituted for intramuscular doses. Peak serum concentrations of interferon beta-1a have been reported to occur 3 hours after subcutaneous injection and between 3 and 15 hours after intramuscular injection, and those for beta-1b have been reported to occur 1 to 8 hours after subcutaneous injection. The elimination half-life for intramuscular interferon beta-1a is about 10 hours. Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avonex; Betaferon; Blastoferon; Rebif; *Austral.*: Avonex; Betaferon; Rebif; *Austria*: Avonex; Betaferon; Extavia; Rebif; *Belg.*: Avonex; Betaferon; Extavia; Rebif; *Braz.*: Avonex; Betaferon; Rebif; Serobif†; *Canad.*: Avonex; Betaseron; Extavia; Rebif; *Chile*: Avonex; Betaferon; Blastoferon; *China*: Betaferon (倍善龙); Rebif (利比); *Cz.*: Avonex; Betaferon; Extavia; Rebif; *Denm.*: Avonex; Betaferon; Extavia; Rebif; *Fin.*: Avonex; Betaferon; Rebif; *Fr.*: Avonex; Betaferon; Extavia; Rebif; *Ger.*: Avonex; Betaferon; Extavia; Fiblaferon†; Rebif; *Gr.*: Avonex; Betaferon; Extavia; Rebif; *Hong Kong*: Betaferon; Rebif; *Hung.*: Avonex; Betaferon; Extavia; Rebif; *India*: Betaferon†; Rebif; *Indon.*: Betaferon; Rebif; *Irl.*: Avonex; Betaferon; Extavia; Rebif; *Israel*: Avonex; Betaferon; Extavia; Rebif; *Ital.*: Avonex; Betaferon; Extavia; Rebif; Serobif†; *Jpn*: Feron; *Malaysia*: Betaferon; Rebif; *Mex.*: Avonex; Betaferon; Emaxem; Jumtab; Rebif; Uribeta; Xerfelan; *Neth.*: Avonex; Betaferon; Extavia; Rebif; *Norw.*: Avonex; Betaferon; Extavia; Rebif; *NZ*: Avonex; Betaferon; Rebif†; *Philipp.*: Betaferon; Rebif; *Pol.*: Avonex; Betaferon; Extavia; Rebif; *Port.*: Avonex; Betaferon; Extavia; Rebif; *Rus.*: Avonex (Авонекс); Betaferon (Бетаферон); Extavia (Экставиа); Genfaxon (Генфаксон); Rebif (Ребиф); Ronbetal (Ронбетал); *S.Afr.*: Avonex; Betaferon; Rebif; *Singapore*: Betaferon; Rebif; *Spain*: Avonex; Betaferon; Extavia; Rebif; *Swed.*: Avonex; Betaferon; Extavia; Rebif; *Switz.*: Avonex; Betaferon; Rebif; *Thai.*: Betaferon; Rebif; *Turk.*: Avonex; Betaferon; Rebif; *UK*: Avonex; Betaferon; Extavia; Rebif; *Ukr.*: β-Imunoferon 1a (β-Иммуноферон 1a); β-Imunoferon 1b (β-Иммуноферон 1b); Avonex (Авонекс); Betpher-1a (Бетфер-1a); Betpher-1b (Бетфер-1b); *USA*: Avonex; Betaseron; Extavia; Rebif; *Venez.*: Avonex; Rebif.

Interferon Gamma *(BAN, rINN)*

IFN-γ; Interferón-γ; Interferon-γ; Interferón gamma; Interféron gamma; Interferoni gamma; Interferonigamma; Interferonum Gamma; Интерферон Гамма.

CAS — 98059-18-8 (interferon gamma-1a); 98059-61-1 (interferon gamma-1b).

ATC — L03AB03.

ATC Vet — QL03AB03.

UNII — 21K6M2I7AG (interferon gamma-1b).

NOTE. Interferon gamma was previously known as immune interferon.

Interferon gamma-1b is *USAN* and was previously known as interferon gamma-2a.

Pharmacopoeias. *Eur.* (see p. vii) includes Interferon Gamma-1b Concentrated Solution.

Ph. Eur. 8: (Interferon Gamma-1b Concentrated Solution; Interferoni Gamma-1b Solutio Concentrata). It is a solution of the *N*-terminal methionyl form of interferon gamma. It is produced by a method based on recombinant DNA technology using bacteria as host cells. It contains a minimum of $30X10^6$ units/mg of protein. A clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of -70 degrees. Protect from light.

Nomenclature. Interferon gamma may be derived from immunologically stimulated T-lymphocytes (hence its former name of immune interferon) or produced by recombinant DNA technology. Similarly to interferon alfa, protein variants of interferon gamma are designated by a number and further qualified by a letter to indicate the amino-acid sequences at terminal positions 1 and 139:

- interferon gamma-1a has at position 1 hydrogen, cysteine, tyrosine, and cysteine and at position 139 arginine, alanine, serine, glutamine, and a hydroxyl group
- interferon gamma-1b, formerly known as interferon gamma-2a, has at position 1 hydrogen and methionine and at position 139 a hydroxyl group

Interferon gamma derived through recombinant DNA technology is labelled (rbe).

Uses and Administration

Interferon gamma is a cytokine with antiviral and immunomodulating effects. Interferon gamma-1b is used for its action as a macrophage-stimulating factor as an adjunct to antimicrobial therapy in chronic granulomatous disease. It is also used to delay time to disease progression and reduce the frequency of serious infections in patients with severe malignant osteopetrosis.

Interferon gamma-1b is given in a dose of 50 micrograms/m^2 body-surface (1 million units/m^2) three times weekly by subcutaneous injection. Patients with a body-surface less than 0.5 m^2 should receive 1.5 micrograms/kg three times weekly.

Interferon gamma-1b is also under investigation for the treatment of idiopathic pulmonary fibrosis (see below).

Interferon gamma-n1 has also been used for the treatment of cutaneous T-cell lymphomas.

Reviews.

1. Marciano BE, *et al.* Long-term interferon-γ therapy for patients with chronic granulomatous disease. *Clin Infect Dis* 2004; 39: 692–9.
2. Errante PR, *et al.* The use of interferon-gamma therapy in chronic granulomatous disease. *Recent Pat Antiinfect Drug Discov* 2008; 3: 225–30.
3. Hastie C. Interferon gamma, a possible therapeutic approach for late-stage prostate cancer? *Anticancer Res* 2008; 28: 2843–9.
4. Miller CH, *et al.* Clinical use of interferon-gamma. *Ann N Y Acad Sci* 2009; 1182: 69–79.
5. Kane A, Yang I. Interferon-gamma in brain tumor immunotherapy. *Neurosurg Clin N Am* 2010; 21: 77–86.

Bacterial infections. In addition to its use to control infections in chronic granulomatous disease, interferon gamma was used with some success as an adjunct to antibacterials in a patient with Whipple's disease[1] but was of no benefit in a study in burn-related infections.[2] For the conventional management of these infections, see Whipple's Disease, p. 213.3 and Skin Infections, p. 207.1.

1. Schneider T, *et al.* Treatment of refractory Whipple disease with interferon-γ. *Ann Intern Med* 1998; 129: 875–7.
2. Wasserman D, *et al.* Interferon-γ in the prevention of severe burn-related infections: a European phase III multicenter trial. *Crit Care Med* 1998; 26: 434–9.

MYCOBACTERIAL INFECTIONS. Experience with interferons for *nontuberculous mycobacterial infections* in patients with AIDS is limited. Interferon gamma given with antimycobacterials has produced beneficial responses in patients with *Mycobacterium avium* complex infections, but produced no response or only a transient response in others given interferon gamma alone.[1-3] Benefit has been see when combined with interleukin-2.[4]

Beneficial responses have also been reported after use of interferon alfa[5] or gamma[6,7] as an adjunct to antimycobacterial therapy in HIV-negative patients with mycobacterial infections unresponsive to conventional therapy. Interferon alfa has been tried as an adjunct to conventional therapy in *multibacillary leprosy.*[8]

Inhaled interferon alfa[9] or gamma[10] may be a useful adjunct to conventional antimycobacterial treatment for *pulmonary tuberculosis.*

For discussion of these infections and their standard treatment, see Leprosy, p. 188.3, Nontuberculous Mycobacterial Infections, p. 194.1, and Tuberculosis, p. 210.2.

1. Squires KE, *et al.* Interferon-γ and Mycobacterium avium-intracellulare infection. *J Infect Dis* 1989; 159: 599–600.
2. Squires KE, *et al.* Interferon-γ treatment for Mycobacterium avium-intracellulare complex bacillemia in patients with AIDS. *J Infect Dis* 1992; 166: 686–7.
3. Lauw FN, *et al.* No beneficial effect of interferon-gamma treatment in 2 human immunodeficiency virus-infected patients with Mycobacterium avium complex infection. *Clin Infect Dis* 2001; 32: e81–e82.
4. Sekiguchi Y, *et al.* Effective combination therapy using interferon-gamma and interleukin-2 for disseminated Mycobacterium avium complex infection in a pediatric patient with AIDS. *Clin Infect Dis* 2005; 41: e104–e106.
5. Maziarz RT, *et al.* Reversal of infection with Mycobacterium avium intracellulare by treatment with alpha-interferon in a patient with hairy cell leukemia. *Ann Intern Med* 1988; 109: 292–4.
6. Holland SM, *et al.* Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma: a preliminary report. *N Engl J Med* 1994; 330: 1348–55.
7. Milanés-Virelles MT, *et al.* Adjuvant interferon gamma in patients with pulmonary atypical mycobacteriosis: a randomized, double-blind, placebo-controlled study. *BMC Infect Dis* 2008; 8: 17. Available at: http://www.biomedcentral.com/content/pdf/1471-2334-8-17.pdf (accessed 26/01/10)
8. Ganapati R, *et al.* A multicenter study of recombinant interferon-alpha2b in the treatment of multibacillary leprosy. *Int J Lepr* 1997; 65: 495–7.
9. Giosuè S, *et al.* Effects of aerosolized interferon-α in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 1998; 158: 1156–62.
10. Condos R, *et al.* Treatment of multidrug-resistant pulmonary tuberculosis with interferon-γ via aerosol. *Lancet* 1997; 349: 1513–15.

Idiopathic pulmonary fibrosis. In a preliminary study[1] in patients with idiopathic pulmonary fibrosis (IPF; see Interstitial Lung Disease, p. 1607.1) who had not responded to treatment with corticosteroids or to other immunosuppressive therapy, lung capacity increased in 9 patients given interferon gamma-1b with prednisolone for 12 months, but deteriorated in 9 who were treated with prednisolone alone for the same period. The study was, however, criticised for its methodology and the statistical significance of its findings questioned.[2] A later study[3] involving 330 patients with IPF found that interferon gamma-1b did not affect progression-free survival or pulmonary function; however, a trend toward lower mortality was seen in patients who received interferon gamma-1b compared with those given placebo. A subsequent study[4] to characterise the molecular effects of subcutaneous interferon gamma-1b versus placebo reported that interferon gamma-1b affected IPF through multiple pathways and could be of potential benefit. A randomised, prospective study[5] comparing interferon gamma-1b and colchicine (given for 24 months) in patients with mild-to-moderate IPF reported that 15.6% of patients treated with interferon gamma-1b and 38.8% of those given colchicine died. Patients treated with interferon gamma-1b also showed a higher forced vital capacity after 24 months of treatment. A review[6] of the use of interferon gamma-1b in the management of CFA found that efficacy of interferon gamma-1b was inconsistent with regard to changes in pulmonary function and mortality, although studies suggested that interferon gamma-1b may be of benefit in earlier-stage disease. A meta-analysis[7] of randomised controlled studies evaluating the use of interferon gamma-1b in the treatment of IPF concluded that interferon gamma-1b therapy was associated with reduced mortality. However, a later large randomised, placebo-controlled study,[8] to assess the effect of interferon gamma-1b on survival in patients with IPF and mild to moderate impairment in their baseline pulmonary function, had to be stopped early after the second interim analysis; after a median treatment duration of 64 weeks, 15% (80/551) of patients on interferon gamma-1b and 13% (35/275) of those on placebo had died.

1. Ziesche R, *et al.* A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 1999; 341: 1264–9.
2. King TE. Interferon gamma-1b for the treatment of idiopathic pulmonary fibrosis. *N Engl J Med* 2000; 342: 974–5.
3. Raghu G, *et al.* A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004; 350: 125–33.
4. Strieter RM, *et al.* Effects of interferon-γ 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; 170: 133–40.
5. Antoniou KM, *et al.* Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; 28: 496–504.
6. Pacanowski MA, Amsden GW. Interferon gamma-1b in the treatment of idiopathic pulmonary fibrosis. *Ann Pharmacother* 2005; 39: 1678–86.
7. Bajwa EK, *et al.* Interferon-γ 1b therapy in idiopathic pulmonary fibrosis: a metaanalysis. *Chest* 2005; 128: 203–6.
8. King TE, *et al.* Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; 374: 222–8.

Leishmaniasis. Interferon gamma has been tried both systemically and locally as an adjunct to standard treatment of leishmaniasis (p. 922.1) with encouraging results. A review[1] of the use of interferon gamma in non-viral infections concluded that interferon gamma was effective when combined with antimony compounds for treatment failures in visceral leishmaniasis (p. 923.1) and could enhance the response to initial therapy in untreated patients. However, the response to adjunctive interferon gamma was limited in patients with a high degree of resistance to antimony compounds.[2] For cutaneous infections (p. 922.1), intralesional interferon gamma has been shown to be effective[3] but less so than intralesional antimony compounds.[4] Subcutaneous interferon gamma (with antimony given intravenously) was no more effective than antimony alone when given as a short course over 10 days.[5] However, encouraging responses have been reported in patients who have failed to respond to antimony compounds alone.[6]

1. Murray HW. Interferon-gamma and host antimicrobial defense: current and future clinical applications. *Am J Med* 1994; 97: 459–67.
2. Sundar S, *et al.* Response to interferon-γ plus pentavalent antimony in Indian visceral leishmaniasis. *J Infect Dis* 1997; 176: 1117–19.
3. Harms G, *et al.* Effects of intradermal gamma-interferon in cutaneous leishmaniasis. *Lancet* 1989; i: 1287–92.
4. Harms G, *et al.* A randomized trial comparing a pentavalent antimonial drug and recombinant interferon-γ in the local treatment of cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1991; 85: 214–16.
5. Arana BA, *et al.* Efficacy of a short course (10 days) of high-dose meglumine antimoniate with or without interferon-γ in treating cutaneous leishmaniasis in Guatemala. *Clin Infect Dis* 1994; 18: 381–4.
6. Falcoff E, *et al.* Clinical healing of antimony-resistant cutaneous or mucocutaneous leishmaniasis following the combined administration of interferon-γ and pentavalent antimonial compounds. *Trans R Soc Trop Med Hyg* 1994; 88: 95–7.

Osteopetrosis. Interferon gamma has been tried in the treatment of malignant osteopetrosis (p. 1609.3). A study[1] in 14 patients found that interferon gamma-1b increased bone resorption. In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

1. Key LL, *et al.* Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med* 1995; 332: 1594–9.

Skin disorders. Interferons have been tried in skin disorders in which IgE levels are raised. Subcutaneous interferon gamma improved *eczema* and reduced serum-IgE concentration in one patient, but the condition gradually returned within a week of stopping treatment.[1] In two studies[2,3] subcutaneous interferon gamma given to patients with severe atopic dermatitis and raised serum-IgE concentrations resulted in improvement of the skin condition; IgE concentrations were reduced in one study[2] but remained high in the other.[3] Subcutaneous interferon alfa, however, was unsuccessful in 2 patients with very severe atopic dermatitis; serum-IgE concentrations and severity of the skin condition remained unaffected.[4] Interferon alfa has been tried in subacute *cutaneous lupus erythematosus*[5,6] and *discoid lupus erythematosus*.[6] Although marked improvement generally occurred, the condition tended to recur within several weeks of stopping treatment. For discussion of the conventional treatment of eczema, see p. 1684.1 and of lupus erythematosus, see Systemic Lupus Erythematosus, p. 1613.3.

There have been reports[7,8] of the successful use of interferon alfa to control the symptoms of *urticaria* associated with mastocytosis (p. 1226.3).

Interferons have also been proposed for antifibrotic therapy in the management of diffuse *scleroderma* (see p. 1942.3). A multicentre study of interferon gamma in scleroderma[9] found that cutaneous symptoms might be improved but that treatment was associated with an unacceptable incidence of adverse effects. Interferon gamma has also been tried in *eosinophilic pustular folliculitis*.[10]

Interferons have also been used for the treatment of warts (see under Interferon Alfa, p. 992.1).

1. Souillet G, *et al.* Alpha-interferon treatment of patient with hyper IgE syndrome. *Lancet* 1989; i: 1384.
2. Reinhold U, *et al.* Recombinant interferon-γ in severe atopic dermatitis. *Lancet* 1990; 335: 1282.
3. Boguniewicz M, *et al.* Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. *Am J Med* 1990; 88: 365–70.
4. MacKie RM. Interferon-α for atopic dermatitis. *Lancet* 1990; 335: 1282–3.
5. Nicolas J-F, Thivolet J. Interferon alfa therapy in severe unresponsive subacute cutaneous lupus erythematosus. *N Engl J Med* 1989; 321: 1550–1.
6. Thivolet J, *et al.* Recombinant interferon α 2a is effective in the treatment of discoid and subacute cutaneous lupus erythematosus. *Br J Dermatol* 1990; 122: 405–9.
7. Kolde G, *et al.* Treatment of urticaria pigmentosa using interferon alpha. *Br J Dermatol* 1995; 133: 91–4.
8. Lippert U, Henz BM. Long-term effect of interferon alpha treatment in mastocytosis. *Br J Dermatol* 1996; 134: 1164–5.
9. Polisson RP, *et al.* A multicenter trial of recombinant human interferon gamma in patients with systemic sclerosis: effects on cutaneous fibrosis and interleukin 2 receptor levels. *J Rheumatol* 1996; 23: 654–8.
10. Fushimi M, *et al.* Eosinophilic pustular folliculitis effectively treated with recombinant interferon-γ: suppression of mRNA expression of interleukin 5 in peripheral blood mononuclear cells. *Br J Dermatol* 1996; 134: 766–72.

Adverse Effects

As for interferons in general (see Interferon Alfa, p. 992.2)

Precautions

As for interferons in general (see Interferon Alfa, p. 995.1). Interferon gamma in high doses has been shown to increase the incidence of abortions in *primates* and should be avoided during pregnancy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies interferon gamma as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

As for interferons in general (see Interferon Alfa, p. 995.2).

Antiviral Action

As for interferons in general (see Interferon Alfa, p. 995.3).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. Peak plasma concentrations of interferon gamma-1b occur about 4 hours after intramuscular injection and about 7 to 8 hours after subcutaneous injection. Half-lives of 38 minutes (intravenous dosage), 2.9 hours (intramuscular dosage), and 4.9 to 5.9 hours (subcutaneous dosage) have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imukin; *Austral.*: Imukin; *Austria*: Imukin; *Belg.*: Immukine; *China*: Gama (伽玛); Lizhu Yindefu (丽珠因得福); Shang Sheng Lei Tai (上生雷泰); *Cz.*: Imukin†; *Denm.*: Imukin; *Fin.*: Imukin; *Fr.*: Imukin; *Ger.*: Imukin; *Gr.*: Imukin; *Hong Kong*: Immukin; *Hung.*: Imukin; *Irl.*: Immukin; *Ital.*: Imukin; *Jpn*: Biogamma†; *Neth.*: Immukine; Imukin†; *Norw.*: Imukin; *NZ*: Imukin; *Port.*: Imukin; *Rus.*: Ingaron (Ингарон); *Singapore*: Imukin; *Spain*: Imukin; *Swed.*: Imukin; *Switz.*: Imukin; *UK*: Immukin; *USA*: Actimmune.

Lamivudine *(BAN, USAN, rINN)*

3TC; GR-109714X; Lamivudiini; Lamivudin; Lamivudina; Lamivudinum; Lamiwudyna; Lavmivudin; Ламивудин; (-)-2′-Deoxy-3′-thiacytidine.

(-)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

$C_8H_{11}N_3O_3S$=229.3

CAS — 131086-21-0; 134678-17-4.

ATC — J05AF05.

ATC Vet — QJ05AF05.

UNII — 2T8Q726O95.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Lamivudine). A white or almost white powder. It exhibits polymorphism. Soluble in water, slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Lamivudine). A white to off-white solid. Soluble in water. Protect from light.

Uses and Administration

Lamivudine is a nucleoside reverse transcriptase inhibitor structurally related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used orally in the treatment of HIV infection and AIDS, (p. 957.2) and chronic hepatitis B infection (p. 952.1). Viral resistance emerges rapidly when lamivudine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

For **HIV infection**, the dose of lamivudine for adults is 300 mg daily as a single dose or in two divided doses.

For chronic **hepatitis B**, the adult dose is 100 mg once daily. In patients with concomitant HIV and hepatitis B infection the dosage regimen appropriate for HIV should be used.

For details of doses in infants, children, and adolescents see below.

Reduction of dosage is recommended for patients with renal impairment (see below).

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing lamivudine in combination with zidovudine or abacavir and with abacavir plus zidovudine are available in some countries.

Reviews.

1. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; 65: 285–302.
2. Shey M, *et al.* A combination drug of abacavir-lamivudine-zidovudine (Trizivir) for treating HIV infection and AIDS. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 14/10/09).
3. Somboonwit C, *et al.* Abacavir and lamivudine combination. *Expert Opin Drug Metab Toxicol* 2009; 5: 1599–1606.
4. Kumar PN, Patel P. Lamivudine for the treatment of HIV. *Expert Opin Drug Metab Toxicol* 2010; 6: 105–14.
5. Achenbach CJ, *et al.* Abacavir/lamivudine fixed-dose combination andretroviral therapy for the treatment of HIV. *Adv Therapy* 2010; 27: 1–16. Correction. *ibid.*; 127.

Administration in children. For the treatment of **HIV infection** in infants and children lamivudine is given orally either as tablets or a solution, with other antiretroviral drugs. Doses are based on body-weight:

- in infants and children over 3 months of age and weighing less than 14 kg or in those unable to swallow tablets the oral solution may be given in a dose of 4 mg/kg twice daily to a maximum daily dose of 300 mg
- in children weighing 14 to 21 kg the tablet formulation may be given in a dose of 75 mg twice daily
- in children weighing 21 to 30 kg the tablet formulation may be given in a dose of 75 mg in the morning and 150 mg at night
- in children weighing over 30 kg the tablet formulation may be given in a dose of 150 mg twice daily

The *BNFC* states that children 1 to 3 months old may be given 4 mg/kg twice daily and that for older children the total daily doses cited above may be given as a single dose once daily.

Dosage of lamivudine should be reduced in HIV-infected patients (at least 3 months of age and weighing less than 30 kg) with moderate to severe *renal impairment* (creatinine clearance (CC) below 50 mL/minute):

- CC 30 to 49 mL/minute: 4 mg/kg for the first dose then 4 mg/kg once daily
- CC 15 to 29 mL/minute: 4 mg/kg for the first dose then 2.6 mg/kg once daily
- CC 5 to 14 mL/minute: 4 mg/kg for the first dose then 1.3 mg/kg once daily
- CC less than 5 mL/minute: 1.3 mg/kg for the first dose then 700 micrograms/kg once daily

For the treatment of chronic **hepatitis B** infection in children and adolescents aged between 2 and 17 years, JS licensed product information recommends an oral dose of lamivudine of 3 mg/kg once daily to a maximum daily dose of 100 mg. Dosage reduction would need to be considered in those with renal impairment. UK licensed product information does not recommend the use of lamivudine for the treatment of chronic hepatitis B in those under 17 years of age.

Administration in renal impairment. Dosage of lamivudine should be reduced in patients with moderate to severe renal impairment (creatinine clearance (CC) below 50 mL/minute).

adults: HIV infection:

- CC 30 to 49 mL/minute: 150 mg for the first dose then 150 mg once daily
- CC 15 to 29 mL/minute: 150 mg for the first dose then 100 mg once daily
- CC 5 to 14 mL/minute: 150 mg for the first dose then 50 mg once daily
- CC less than 5 mL/minute: 50 mg for the first dose then 25 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

adults: chronic hepatitis B infection:

- CC 30 to 49 mL/minute: 100 mg for the first dose then 50 mg once daily
- CC 15 to 29 mL/minute: 100 mg for the first dose then 25 mg once daily
- CC 5 to 14 mL/minute: 35 mg for the first dose then 15 mg once daily
- CC less than 5 mL/minute: 35 mg for the first dose then 10 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

children:

- see Administration in Children, above

Hepatitis. Lamivudine is one of the antivirals being used as an alternative to interferon alfa in the treatment of chronic hepatitis B (p. 952.1).[1-3] In a preliminary study, lamivudine 100 or 300 mg daily reduced hepatitis B virus DNA to low or undetectable levels.[4] In a 1-year double-blind study involving about 350 patients with chronic hepatitis B, lamivudine 100 mg daily was associated with substantial histological improvement in many patients; a dose of 25 mg daily was less effective.[5] Relapses have been reported once treatment with lamivudine is stopped, and a case of reactivation of hepatitis B infection has been reported.[6] Lamivudine has also been used[7] with thymalfasin (p. 2630.1); the combination may be more effective than lamivudine alone. Lamivudine may also be effective in preventing re-infection with hepatitis B in patients during chemotherapy[8-10] and in those who have had liver transplants,[11,12] and beneficial responses have been seen in transplant patients with acute hepatitis B infection treated with lamivudine 100 mg daily for prolonged periods.[13]

1. Dienstag JL, *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; 341: 1256–63.
2. Hagmeyer KO, Pan Y-Y. Role of lamivudine in the treatment of chronic hepatitis B virus infection. *Ann Pharmacother* 1999; 33: 1104–12.
3. Jonas MM, *et al.* Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; 346: 1706–13. Correction. *ibid.*; 347: 975.
4. Dienstag JL, *et al.* A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995; 333: 1657–61.
5. Lai C-L, *et al.* A one-year trial of lamivudine for chronic hepatitis B *N Engl J Med* 1998; 339: 61–8.
6. Honkoop P, *et al.* Hepatitis B reactivation after lamivudine. *Lancet* 1995; 346: 1156–7.
7. Zhang YY, *et al.* Treatment with lamivudine versus lamivudine and thymosin alpha-1 for e antigen-positive chronic hepatitis B patients a meta-analysis. *Virol J* 2009; 6: 63.
8. Yeo W, *et al.* Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 2004; 22: 927–34.
9. Idilman R. Lamivudine prophylaxis in HBV carriers with haematological malignancies who receive chemotherapy. *J Antimicrob Chemother* 2005; 55: 828–31.
10. Loomba R, *et al.* Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; 148: 519–28. Correction. *ibid.* 2009; 150: 657–8.
11. Grellier L, *et al.* Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996; 348: 1212–5. Correction. *ibid.* 1997; 349: 364.

12. Perrillo RP, *et al.* A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; 33: 424–32.
13. Andreone P, *et al.* Lamivudine treatment for acute hepatitis B after liver transplantation. *J Hepatol* 1998; 29: 985–9.

HIV infection and AIDS. Lamivudine is a potent inhibitor of HIV-1 and HIV-2 *in vitro*, including variants resistant to zidovudine.[1] Resistance emerges rapidly when lamivudine is given alone to patients with HIV infections,[2] although sustained responses have been reported despite the emergence of resistance.[3] As discussed on p. 957.2, NRTIs, including lamivudine, are now used in combination antiretroviral drug regimens for the management of HIV infection, typically with one other NRTI and either a NNRTI or an HIV-protease inhibitor.

Lamivudine is also used in prophylactic regimens after occupational exposure to HIV infection and has been tried for reducing vertical transmission from mother to neonate;[4,5] for further information see p. 959.1.

1. Anonymous. Lamivudine: impressive benefits in combination with zidovudine. *WHO Drug Inf* 1996; 10: 5–7.
2. Wainberg MA, *et al.* Development of HIV-1 resistance to (-)2'-deoxy-3'-thiacytidine in patients with AIDS or advanced AIDS-related complex. *AIDS* 1995; 9: 351–7.
3. Ingrand D, *et al.* Phase I/II study of 3TC (lamivudine) in HIV-positive, asymptomatic or mild AIDS-related complex patients: sustained reduction in viral markers. *AIDS* 1995; 9: 1323–9.
4. Mandelbrot L, *et al.* Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; 285: 2083–93.
5. The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002; 359: 1178–86.

Adverse Effects

Lamivudine is generally very well tolerated. However, adverse effects that may be associated with lamivudine either as monotherapy or with other antiretrovirals for the treatment of HIV include abdominal pain, nausea, vomiting, diarrhoea, headache, fever, rash, alopecia, malaise, insomnia, cough, nasal symptoms, arthralgia, and musculoskeletal pain. There have also been reports of pancreatitis, anaemia, neutropenia, and thrombocytopenia. Increases in liver enzymes and serum amylase may occur. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been reported during treatment with nucleoside reverse transcriptase inhibitors.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including lamivudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including lamivudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia, but this may be less likely with lamivudine than with other NRTIs such as didanosine, stavudine, or zalcitabine. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Patients taking a lower dose of lamivudine for the treatment of chronic hepatitis B often have abdominal discomfort and pain, diarrhoea, fatigue, headache, nausea, malaise, respiratory-tract infections, and vomiting. The most frequently reported laboratory abnormalities are elevated creatine phosphokinase, increases in serum lipase, and raised liver enzymes, in particular alanine aminotransferase. There have been rare reports of lactic acidosis, pancreatitis, and muscle disorders such as cramps, myalgia, and rhabdomyolysis.

Effects on the blood. Although anaemia associated with lamivudine usually occurs when it is used with zidovudine, there has been a report[1] of severe anaemia in a 62-year-old HIV-infected man given lamivudine alone.

1. Weitzel T, *et al.* Severe anaemia as a newly recognized side-effect caused by lamivudine. *AIDS* 1999; 13: 2309–11.

Effects on the hair. Hair loss was associated with lamivudine treatment in 5 patients.[1]

1. Fong IW. Hair loss associated with lamivudine. *Lancet* 1994; 344: 1702.

Effects on the nervous system. Exacerbation of peripheral neuropathy has been reported in a patient after substitution of lamivudine for zalcitabine.[1] A severe exacerbation, associated with mitochondrial toxicity and eventual death, has also been reported in a patient with previously mild neuropathy, occurring 3 months after starting lamivudine for treatment of hepatitis.[2]

1. Cupler EJ, Dalakas MC. Exacerbation of peripheral neuropathy by lamivudine. *Lancet* 1995; 345: 460–1.
2. Podale V, *et al.* Fatal exacerbation of peripheral neuropathy during lamivudine therapy: evidence for iatrogenic mitochondrial damage. *Anaesthesia* 2005; 60: 806–10.

Hypersensitivity. Angioedema, urticaria, and anaphylactoid reaction occurred in a patient 30 minutes after receiving the first dose of lamivudine.[1]

1. Kainer MA, Mijch A. Anaphylactoid reaction, angioedema, and urticaria associated with lamivudine. *Lancet* 1996; 348: 1519.

Precautions

Lamivudine therapy should be stopped in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded.

Treatment with lamivudine may be associated with lactic acidosis and should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, or metabolic or lactic acidosis of unknown aetiology. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Patients co-infected with HIV and chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In patients with chronic hepatitis B, there is a risk of rebound hepatitis when lamivudine is stopped, and liver function should be monitored in such patients. The possibility of HIV infection should be excluded before beginning lamivudine therapy for hepatitis B, since the lower doses used to treat the latter may permit the development of lamivudine-resistant strains of HIV.

Dosage reduction may be necessary in patients with impaired renal function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lamivudine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

The renal excretion of lamivudine may be inhibited by other drugs mainly eliminated by active renal secretion, for example trimethoprim. Usual prophylactic doses of trimethoprim are unlikely to necessitate reductions in lamivudine dosage unless the patient has renal impairment, but the co-administration of lamivudine with the high doses of trimethoprim (as co-trimoxazole) used in pneumocystis pneumonia and toxoplasmosis should be avoided. Although there is usually no clinically significant interaction with zidovudine, severe anaemia has occasionally been reported in patients given lamivudine with zidovudine (see Zidovudine, Interactions, p. 1026.3). Lamivudine may antagonise the antiviral action of zalcitabine and the two drugs should not be used together. Once daily triple nucleoside regimens of lamivudine and tenofovir with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should be avoided.

Antineoplastics. For a reported interaction between lamivudine and *cladribine*, see p. 769.2.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals, see Stavudine, p. 1016.2.

Antiviral Action

Lamivudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Lamivudine is also active against hepatitis B virus. Resistance to lamivudine has been reported in isolates of HIV and hepatitis B virus.

Pharmacokinetics

Lamivudine is rapidly absorbed after oral doses and peak plasma concentrations occur in about 1 hour. Absorption is delayed, but not reduced, by ingestion with food. Bioavailability is between 80 and 87%. Binding to plasma protein is reported to be up to 36%. Lamivudine crosses the blood-brain barrier with a ratio of CSF to serum concentrations of about 0.12. It crosses the placenta and is distributed into breast milk.

Lamivudine is metabolised intracellularly to the active antiviral triphosphate. Hepatic metabolism is low and it is cleared mainly unchanged by active renal excretion. An elimination half-life of 5 to 7 hours has been reported after a single dose.

References.
1. Mueller BU, *et al.* Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1998; 42: 3187–92.
2. Johnson MA, *et al.* Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet* 1999; 36: 41–66.
3. Bruno R, *et al.* Comparison of the plasma pharmacokinetics of lamivudine during twice and once daily administration in patients with HIV. *Clin Pharmacokinet* 2001; 40: 695–700.
4. Asari A, *et al.* Pharmacokinetics of lamivudine in subjects receiving peritoneal dialysis in end-stage renal failure. *Br J Clin Pharmacol* 2007; 64: 738–44.
5. Burger DM, *et al.* Age-dependent pharmacokinetics of lamivudine in HIV-infected children. *Clin Pharmacol Ther* 2007; 81: 517–20.
6. Tremoulet AH, *et al.* Pediatric AIDS Clinical Trials Group. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; 51: 4297–4302.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: 3TC; Amilitrap; Ganvirel; Heptodine; Imunoxa†; Kess; Lamibergen; Lamilea; Oralmuv; Ultraviral†; Vuclodir; *Austral.*: 3TC; Zeffix; *Austria*: Epivir; Zeffix; *Belg.*: Epivir; Zeffix; *Braz.*: Epivir; Lami; Vudirax; *Canad.*: 3TC; Heptovir; *Chile*: 3TC/Epivir; *China*: Epivir (益平维); Heptodin (贺普丁); *Cz.*: Epivir; Zeffix; *Denm.*: Epivir; Zeffix; *Fin.*: Epivir; Zeffix; *Fr.*: Epivir; Zeffix; *Ger.*: Epivir; Kivexa; Zeffix; *Gr.*: Epivir; Zeffix; *Hong Kong*: 3TC; Zeffix; *Hung.*: Epivir; Zeffix; *India*: Hepavud; Hepitec; Ladiwin; Lamda; Lami; Lamidac; Lamivir; Lamivox; Lamuvid; Lavir; Lazid; *Indon.*: 3TC-HBV; 3TC; *Irl.*: Epivir; Zeffix; *Israel*: Epivir; Zeffix; *Ital.*: Epivir; Zeffix; *Jpn*: Epivir; *Malaysia*: 3TC; Zeffix; *Mex.*: 3TC; *Neth.*: Epivir; Zeffix; *Norw.*: Epivir; Zeffix; *NZ*: 3TC; Zeffix; *Philipp.*: Zeffix; *Pol.*: Epivir; Zeffix; *Port.*: Epivir; Zeffix; *Rus.*: Epivir (Эпивир); Zeffix (Зеффикс); *S.Afr.*: 3TC; Legram; *Singapore*: Epivir; Zeffix; *Spain*: Epivir; Zeffix; *Swed.*: Epivir; Zeffix; *Switz.*: 3TC; Zeffix; *Thai.*: Epivir; Lahep; Lamivir; Zeffix; *Turk.*: Epivir; Medovir; Mivux; Zeffix; Zefomen; *UK*: Epivir; Zeffix; *USA*: Epivir; *Venez.*: Epivir; Lamivir.

Multi-ingredient Preparations. *Arg.*: 3TC Complex; 3TC/AZT†; Ganvirel Duo; Imunoxa Complex†; Kess Complex; Kivexa; Lazinevir; Muvidina; Tricivir; Trilaxis; Trivudin; Ultraviral Duo†; Zetavudin; Zidomuv; *Austral.*: Combivir; Kivexa; Trizivir; *Austria*: Combivir; Kivexa; Trizivir; *Belg.*: Combivir; Kivexa; Trizivir; *Braz.*: Biovir; Kivexa; Zidolam; *Canad.*: Combivir; Kivexa; Trizivir; *Chile*: Combivir; Kivexa; Tricivir; *China*: Combivir (双汰芝); Trizivir (三协唯); *Cz.*: Combivir; Kivexa; Trizivir; *Denm.*: Combivir; Kivexa; Trizivir; *Fin.*: Combivir; Kivexa; Trizivir; *Fr.*: Combivir; Kivexa; Trizivir; *Ger.*: Combivir; Trizivir; *Gr.*: Combivir; Kivexa; Trizivir; *Hong Kong*: Combivir; Kivexa; Trizivir; *Hung.*: Combivir; Kivexa; Trizivir; *India*: Combivir; Cytocom-E; Cytocom-N; Cytocom; Duovir N; Duovir-E; Duovir; Emduo-E; Emduo-N; Emduo; Emtri; Lamda-Z; Lami Plus; Lamivir S; Lamostad-N; Lamostad; Lamsyn-Z; Lamuzid; Lazid-E; Lazid-N; Odivir Kit; Triomune; *Irl.*: Combivir; Kivexa; Trizivir; *Israel*: Combivir; Kivexa; Trizivir; *Ital.*: Combivir; Kivexa; Trizivir; *Malaysia*: Combivir; *Mex.*: Combivir; Kivexa; Trizivir; *Neth.*: Combivir; Kivexa; Trizivir; *Norw.*: Combivir; Kivexa; Trizivir; *NZ*: Combivir; Kivexa; Trizivir; *Philipp.*: Combivir; *Pol.*: Combivir; Kivexa; Trizivir; *Port.*: Combivir; Kivexa; Trizivir; *Rus.*: Combivir (Комбивир); Kivexa (Кивекса); Trizivir (Тризивир); *S.Afr.*: Cipla-Duovir; Colamzivy; Combivir; Combozil; Kivexa; Lamzid; Lodiz; Retrovir/3TC Post-HIV Exposure; Sonke Abadamizid; Sonke-LamiNevStav; Triomune; Trizivar; Virtrium; *Singapore*: Combivir; Kivexa; Trizivir; *Spain*: Combivir; Kivexa; Trizivir; *Swed.*: Combivir; Kivexa; Trizivir; *Switz.*: Combivir; Kivexa; Trizivir; *Thai.*: Combid; GPO-Vir S; GPO-Vir Z; Kivexa; La-Stavir; Zilavir; Zovilam; *Turk.*: Combivir; Trizivir; *UK*: Combivir; Kivexa; Trizivir; *USA*: Combivir; Epzicom; Trizivir; *Venez.*: Combivir; Duovir; Triomune; Trizivir.

Pharmacopoeial Preparations

BP 2014: Lamivudine Tablets; Zidovudine and Lamivudine Tablets;
USP 36: Lamivudine and Zidovudine Tablets; Lamivudine Oral Solution.

Laninamivir *(rINN)*

Laninamivirum; R-125489; Ланинамивир.
(2*R*,3*R*,4*S*)-3-Acetamido-2-[(1*R*,2*R*)-2,3-dihydroxy-1-methoxypropyl]-4-guanidino-3,4-dihydro-2*H*-pyran-6-carboxylic acid.
$C_{13}H_{22}N_4O_7$=346.3.
CAS — 203120-17-6.
UNII — B408IW3GL5.

The symbol † denotes a preparation no longer actively marketed

Laninamivir Octanoate (rINNM)

CS-8958; Laninamivir Octanoate Hydrate; (2*R*,3*R*,4*S*)-3-Acetamido-4-guanidino-2-[(1*R*,2*R*)-2-hydroxy-1-methoxy-3-(octanoyloxy)propyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid monohydrate.

$C_{21}H_{36}N_4O_8.H_2O$=490.6.

CAS — 203120-46-1 (anhydrous laninamivir octanoate); 371755-92-9 (laninamivir octanoate hydrate).

Profile

Laninamivir octanoate is the prodrug of laninamivir, a long-acting neuraminidase inhibitor available in Japan for the treatment of influenza A and B, (p. 960.2) including oseltamivir-resistant and pandemic (H1N1) 2009 influenza viruses. It is given as a single dose of 40 mg by oral inhalation; children may be given 20 mg.

References.
1. Watanabe A, *et al.* Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: a double-blind, randomized, noninferiority clinical trial. *Clin Infect Dis* 2010; 51: 1167–75.
2. Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. *Antimicrob Agents Chemother* 2010; 54: 2575–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Inavir.

Lopinavir (BAN, USAN, rINN)

A-157378.0; ABT-378; Lopinaviir; Lopinavirum; Лопинавир.

(αS)-Tetrahydro-*N*-((αS)-α-[(2*S*,3*S*)-2-hydroxy-4-phenyl-3-[2-(2,6-xylyloxy)acetamido]butyl]phenethyl)-α-isopropyl-2-oxo-1(2*H*)-pyrimidineacetamide.

$C_{37}H_{48}N_4O_5$=628.8

CAS — 192725-17-0.

ATC — J05AE06.

ATC Vet — QJ05AE06.

UNII — 2494G1JF75.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lopinavir). A white or yellowish-white, slightly hygroscopic powder. It shows polymorphism. Practically insoluble in water; very soluble in methyl alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Lopinavir). A white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol; soluble in isopropyl alcohol. Store in airtight containers.

Uses and Administration

Lopinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is formulated with low-dose ritonavir, which acts as a pharmacokinetic enhancer. The combination is used in the treatment of HIV infection and AIDS (p. 957.2). Ritonavir-boosted lopinavir is also recommended for HIV postexposure prophylaxis (p. 959.1). Viral resistance emerges rapidly when ritonavir-boosted lopinavir is used alone, and it is therefore used with other antiretrovirals.

The oral dose in treatment-naive and -experienced adults is lopinavir 400 mg (with ritonavir 100 mg) twice daily. Alternatively, a once-daily dose of lopinavir 800 mg (with ritonavir 200 mg) may be considered for patients having only very few (less than 3) HIV-protease inhibitor-associated resistance mutations.

US licensed product information recommends that if the tablets are given in a treatment regimen with either *amprenavir, nelfinavir, efavirenz,* or *nevirapine* consideration be given to increasing the dose of lopinavir to 500 mg (with ritonavir 125 mg) twice daily. For patients taking the oral solution in such regimens the dose should be increased to lopinavir 533 mg (with ritonavir 133 mg) twice daily. When used with any of these drugs, the once-daily regimen of lopinavir should not be used.

Lopinavir film-coated tablets may be taken with or without food; the soft capsules and solution should be taken with food.

For a discussion of dosing in pregnant women, see Pregnancy under Pharmacokinetics, p. 1003.1.

For details of doses in children, see below.

Reviews.
1. Oldfield V, Plosker GL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs* 2006; 66: 1275–99.
2. Schechter M, Nunes EP. Monotherapy with lopinavir/ritonavir. *Expert Opin Invest Drugs* 2007; 16: 735–41.
3. Barragan F, Podzamczer D. Lopinavir/ritonavir: a protease inhibitor for HIV-1 treatment. *Expert Opin Pharmacother* 2008; 9: 2363–75.
4. Croxtall JD, Perry CM. Lopinavir/ritonavir: a review of its use in the management of HIV-1 infection. *Drugs* 2010; 70: 1885–1915.

Administration in children. For the treatment of HIV infection in children, ritonavir-boosted lopinavir is given twice daily with other antiretroviral drugs. The US licensed product information permits use in infants as young as 14 days old, whereas in the UK the age is 2 years. The dose given should not exceed the maximum adult dose (see above).

In the UK the use of the oral solution is preferred to the tablets as a more accurate dose may be given. Doses are based on body-surface.

- In children 2 years of age or more the recommended dose of the *oral solution* is lopinavir 230 mg/m² (with ritonavir 57.5 mg/m²) twice daily with food. A dose increase to 300 mg/m² (with ritonavir 75 mg/m²) twice daily with food should be considered when given with *efavirenz* or *nevirapine*

In the USA the dose is based on body-weight or body-surface as follows:

- given without interacting antiretrovirals
  - 14 days to 6 months of age: lopinavir 16 mg/kg (with ritonavir 4 mg/kg) twice daily or lopinavir 300 mg/m² (with ritonavir 75 mg/m²) twice daily
  - 6 months or older and less than 15 kg: lopinavir 12 mg/kg (with ritonavir 3 mg/kg) twice daily or lopinavir 230 mg/m² (with ritonavir 57.5 mg/m²) twice daily
  - 15 to 40 kg: lopinavir 10 mg/kg (with ritonavir 2.5 mg/kg) twice daily or lopinavir 230 mg/m² (with ritonavir 57.5 mg/m²) twice daily
  - over 40 kg: normal adult dose
- given in a treatment regimen with either *amprenavir, efavirenz, nelfinavir,* or *nevirapine* (requiring the dose of lopinavir/ritonavir to be increased):
  - 6 months or older and less than 15 kg: lopinavir 13 mg/kg (with ritonavir 3.25 mg/kg) twice daily or lopinavir 300 mg/m² (with ritonavir 75 mg/m²) twice daily
  - 15 to 45 kg: lopinavir 11 mg/kg (with ritonavir 2.75 mg/kg) twice daily or lopinavir 300 mg/m² (with ritonavir 75 mg/m²) twice daily
  - over 45 kg: as for adults, above

It has been suggested that HIV-protease inhibitor experienced children may have inadequate drug exposure on standard doses of ritonavir-boosted lopinavir; for further information, see under Pharmacokinetics, p. 1003.1.

SARS. In a preliminary open study[1] 41 patients with probable SARS were given ritonavir-boosted lopinavir as well as the local standard treatment of ribavirin and corticosteroids. At 21 days there was improved outcome with reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections.

1. Chu CM, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; 59: 252–6.

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing lopinavir (formulated with ritonavir) is diarrhoea of mild to moderate severity. Pancreatitis has been seen in patients receiving lopinavir, including those who developed marked triglyceride elevations; in some cases fatalities have occurred. Severe, and in some cases fatal hepatotoxicity has also been reported in patients given ritonavir-boosted lopinavir, particularly in the setting of pre-existing chronic liver disease. Other commonly reported adverse effects include asthenia, headache, insomnia, pain, paraesthesia, gastrointestinal disturbances, acne, and rash. Abnormal laboratory test results associated with lopinavir-containing regimens include increases in serum cholesterol and triglycerides and raised liver enzymes. ECG abnormalities such as prolongation of the PR interval, in some cases progressing to second- and third-degree AV block, have occurred in some patients; QT-interval prolongation and torsade de pointes have also been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including lopinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including lopinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during treatment with ritonavir-boosted lopinavir. Such therapy should be stopped if symptoms of pancreatitis occur.

Patients with pre-existing liver dysfunction or marked elevated liver enzymes are at increased risk for further hepatotoxicity and should be monitored carefully; stopping treatment should be considered if there is evidence of worsening liver function. In the UK, ritonavir-boosted lopinavir is contra-indicated in patients with severe hepatic impairment.

Due to the potential for ECG abnormality and potential cardiac arrhythmia, ritonavir-boosted lopinavir should be used with caution in patients with underlying heart disease or conduction system abnormalities, or in those using other drugs known to prolong the PR interval. Use should also be avoided in those with congenital long-QT syndrome, hypokalaemia, or using other QT-interval prolonging drugs.

The oral solution (*Kaletra, Abbott*) has a high content of alcohol and propylene glycol, present as excipients, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further information on propylene glycol toxicity, see Adverse Effects and Precautions, p. 2205.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lopinavir as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Licensed product information notes that in *rats* given toxic doses of ritonavir-boosted lopinavir, there was early resorption, decreased fetal viability and body weight, and an increased incidence of skeletal variation and delayed skeletal ossification in the offspring. However, US guidelines[1] for the use of antiretroviral drugs in pregnant HIV-infected women note that there appears to be no evidence of human teratogenicity, and consider ritonavir-boosted lopinavir to be a drug of choice for use in HIV drug regimens required during pregnancy (see under Indinavir, p. 987.1). For evidence that doses should be increased during the latter part of pregnancy see under Pharmacokinetics, p. 1003.1.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2011). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Lopinavir is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It is formulated with low-dose ritonavir, which inhibits this enzyme and thus increases its exposure. The combination is an inhibitor of CYP3A4 and increases plasma concentration of drugs mainly metabolised by this isoenzyme. It has also been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolised by cytochrome P450 isoenzymes and by glucuronidation. Drugs that strongly induce CYP3A4 may result in decreased plasma concentrations of the combination.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted lopinavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- antihistamines (astemizole and terfenadine)
- antipsychotics (*pimozide*)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA licensed product information also contra-indicates use with the alpha$_1$-adrenoceptor antagonist alfuzosin. Owing to the potential for increased serum concentrations of sildenafil, ritonavir-boosted lopinavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir-boosted lopinavir may increase serum

concentrations of inhaled salmeterol and the combination is not recommended. Rifampicin and St John's wort decrease the concentration of lopinavir; use with the antiretroviral is best avoided due to the possible loss of its activity and development of resistance. UK licensed product information contra-indicates the use of vardenafil and amiodarone with ritonavir-boosted lopinavir.

When ritonavir-boosted lopinavir is used with some other antiretrovirals (such as efavirenz, nevirapine, amprenavir/fosamprenavir, and nelfinavir), decreased concentrations of lopinavir may occur. In some cases this may result in the need for dose modification (see p. 1002.1). Use with ritonavir-boosted fosamprenavir or tipranavir is not recommended.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antibacterials. Although *rifabutin* may reduce the plasma concentrations of some HIV-protease inhibitors (see under Indinavir, p. 987.3), a retrospective study[1] found an association between use of rifabutin with ritonavir-boosted lopinavir and *increased* plasma-lopinavir concentrations.

1. Stöhr W, *et al.* UK CHIC Steering Committee. Factors influencing lopinavir and atazanavir plasma concentration. *J Antimicrob Chemother* 2010; **65**: 129–37.

Antiviral Action

Lopinavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Lopinavir is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur after 4 hours. Bioavailability is enhanced when given with a high fat meal. Lopinavir is reported to be 98 to 99% bound to serum proteins. Lopinavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme CYP3A4; 13 metabolites have been identified with some, such as 4-oxylopinavir and 4-hydroxylopinavir, having antiviral activity. Lopinavir is mainly excreted in faeces and to a smaller extent in the urine; unchanged lopinavir accounts for about 2.2% of a dose excreted in the urine and 19.8% in the faeces. After multiple dosing, less than 3% of the absorbed lopinavir dose is excreted unchanged in the urine. The terminal elimination half-life of lopinavir is reported to be about 5 to 6 hours.

Children. The pharmacokinetics of lopinavir have been reported to vary greatly during childhood, with decreased drug exposure a concern in certain subpopulations.[1] Although there is clinical evidence for good antiviral efficacy of ritonavir-boosted lopinavir in children at the recommended standard doses, a pharmacokinetic model[2] of lopinavir in children 4 years of age and older has suggested that, although these doses are likely to be sufficient for children infected with wild-type virus, they may not provide adequate inhibitory concentrations for even moderately resistant HIV; the authors suggested that HIV-protease inhibitor experienced children might therefore benefit from routine monitoring of serum drug levels and evaluations for resistance.

1. Jullien V, *et al.* Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother* 2006; **50**: 3548–55.
2. Rakhmanina N, *et al.* Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2009; **53**: 2532–8.

Pregnancy. Due to the lack of data addressing whether serum-drug concentrations of the tablet formulation are adequate, US guidelines[1] recommend that once-daily ritonavir-boosted lopinavir dosing regimens be avoided in pregnant women. A twice-daily dose regimen should be used; and while some experts advocate the use of standard doses (see Uses and Administration, p. 1002.1) with serum concentration monitoring, empirical use of increased doses have been recommended by others.

A small study[2] in pregnant patients suggested that an increased dose of the tablet formulation of ritonavir-boosted lopinavir (a twice-daily dose of 600 mg of lopinavir with 150 mg of ritonavir) was needed during the second and third trimesters of pregnancy in order to provide equivalent exposure to that seen in non-pregnant patients taking usual doses of 400 mg of lopinavir with 100 mg ritonavir twice daily. The dose could be reduced to standard dosage within 2 weeks of delivery.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)
2. Best BM, *et al.* International Maternal Pediatric Adolescent AIDS Clinical Trials Group 1026s Study Team. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr* 2010; **54**: 381–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Kaletra; ***Austral.***: Kaletra; ***Austria***: Kaletra; ***Belg.***: Kaletra; ***Braz.***: Kaletra; ***Canad.***: Kaletra; ***Chile***: Kaletra; ***China***: Aluvia (克力芝); ***Cz.***: Kaletra; ***Denm.***: Kaletra; ***Fin.***: Kaletra; ***Fr.***: Kaletra; ***Ger.***: Kaletra; ***Gr.***: Kaletra; ***Hong Kong***: Kaletra; ***Hung.***: Kaletra; ***India***: Emletra; Lopimune; Ritomax-L; ***Irl.***: Kaletra; ***Israel***: Kaletra; ***Ital.***: Kaletra; ***Malaysia***: Kaletra; ***Mex.***: Kaletra; ***Neth.***: Kaletra; ***Norw.***: Kaletra; ***NZ***: Kaletra; ***Pol.***: Kaletra; ***Port.***: Kaletra; ***Rus.***: Kaletra (Калетра); ***S. Afr.***: Aluvia; Kaletra; ***Singapore***: Kaletra; ***Spain***: Kaletra; ***Swed.***: Kaletra; ***Switz.***: Kaletra; ***Thal.***: Aluvia; Kaletra; ***Turk.***: Kaletra; ***UK***: Kaletra; ***USA***: Kaletra; ***Venez.***: Kaletra.

Pharmacopoeial Preparations
USP 36: Lopinavir and Ritonavir Tablets.

Maraviroc *(BAN, USAN, rINN)*

Maravirocum; Maravirok; Marawirok; UK-427857; Маравирок.

4,4-Difluoro-*N*-[(1*S*)-3-[(1*R*,3*s*,5*S*)-3-[3-methyl-5-(propan-2-yl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octan-8-yl]-1-phenylpropyl]cyclohexanecarboxamide.

$C_{32}H_{41}F_2N_5O$=513.7

CAS — 376348-65-1.

ATC — J05AX09.

ATC Vet — QJ05AX09.

UNII — MD6P741W8A.

Uses and Administration

Maraviroc is an antagonist of the CCR5 chemokine receptor (see Antiviral Action, below). It is used, with other antiretrovirals, for the treatment of HIV infection and AIDS (p. 957.2) in adult patients with exclusively CCR5-tropic HIV-1 infection. Co-receptor tropism should be determined by specific testing before maraviroc is used.

Maraviroc is given orally in a dose of 300 mg twice daily, although dose adjustments may be needed depending on interactions with other medicines; recommendations for these may vary, but for guidance the following doses have been recommended in the UK or USA:

- For patients also taking potent CYP3A4 inhibitors such as HIV-protease inhibitors (other than ritonavir-boosted fosamprenavir or tipranavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin, the recommended dose is 150 mg twice daily. These reductions generally apply even if a CYP3A4 inducer such as efavirenz or etravirine is also being given.
- In those whose therapy includes CYP3A4 inducers such as efavirenz, rifampicin, carbamazepine, phenobarbital, and phenytoin *without* a CYP3A4 inhibitor, the recommended dose is 600 mg twice daily.
- Patients taking other antiretrovirals (including ritonavir-boosted fosamprenavir or tipranavir), or other drugs, may be given the standard dose of 300 mg twice daily.

Licensed doses in the USA are generally similar to those in the UK, but US licensed product information does not exclude ritonavir-boosted fosamprenavir from the drugs considered to be potent inhibitors of CYP3A4; therefore the recommended dose of maraviroc when they are given together is 150 mg twice daily.

References.
1. Carter NJ, Keating GM. Maraviroc. *Drugs* 2007; **67**: 2277–88.
2. Vandekerckhove L, *et al.* Maraviroc: integration of a new antiretroviral drug class into clinical practice. *J Antimicrob Chemother* 2008; **61**: 1187–90.
3. MacArthur RD, Novak RM. Maraviroc: the first of a new class of antiretroviral agents. *Clin Infect Dis* 2008; **47**: 236–41.
4. Dau B, Holodniy M. Novel targets for antiretroviral therapy: clinical progress to date. *Drugs* 2009; **69**: 31–50.
5. Yost R, *et al.* Maraviroc: a coreceptor CCR5 antagonist for management of HIV infection. *Am J Health-Syst Pharm* 2009; **66**: 715–26.
6. Perry CM. Maraviroc: a review of its use in the management of CCR5-tropic HIV-1 infection. *Drugs* 2010; **70**: 1189–1213.

Administration in renal impairment. UK licensed product information recommends that the oral dose of maraviroc be adjusted in patients with renal impairment who are also taking potent inhibitors of cytochrome P450 isoenzyme CYP3A4. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- For patients also taking potent CYP3A4 inhibitors such as ritonavir-boosted HIV-protease inhibitors (other than fosamprenavir or tipranavir), ketoconazole, itraconazole, clarithromycin, and telithromycin and who have a CC < 80 mL/minute: 150 mg every 24 hours
- For patients also taking ritonavir-boosted fosamprenavir who have a CC < 80 mL/minute: 150 mg every 12 hours

Alternatively, US licensed product information has recommended that patients taking potent CYP3A inhibitors (including ritonavir-boosted fosamprenavir) with or without a CYP3A inducer, who have a CC of 30 to 80 mL/minute should be given a dose of 150 mg twice daily. Maraviroc is not recommended in patients with CC < 30 mL/minute who are taking potent CYP3A inhibitors or inducers.

Although dose adjustment is generally not recommended for renal impairment in patients not using potent CYP3A inhibitors or inducers, US licensed product information recommends that patients with CC < 30 mL/minute who have orthostatic hypotension while taking maraviroc should have their dose reduced to 150 mg twice daily.

No adjustment is necessary when maraviroc is given without potent CYP3A4 inhibitors or with tipranavir.

Adverse Effects and Precautions

On the basis of limited data, maraviroc appears to be well tolerated; non-specific adverse effects associated with maraviroc-based regimens include asthenia, cough and upper respiratory-tract infections, dizziness, abdominal pain and distension, constipation, diarrhoea, dyspepsia, nausea, vomiting, fever, headache, insomnia, somnolence, muscle spasms and back pain, pruritus, and rash. Less frequently reported adverse effects include bone marrow depression, myositis and rhabdomyolysis, osteonecrosis, and cardiovascular effects such as myocardial ischaemia and myocardial infarction; cardiac adverse effects were reported mainly for patients with pre-existing cardiac disease or risk factors. Maraviroc should be used cautiously in patients with a history of orthostatic hypotension, or those on blood pressure lowering medications.

Hepatobiliary disorders, including hepatic cirrhosis, cholestatic jaundice, and portal vein thrombosis have occurred rarely. Hepatotoxicity, sometimes preceded by evidence of systemic allergic reaction, has also been reported; stopping maraviroc should be considered in patients with signs or symptoms of hepatitis, or increased liver transaminases with rash or other systemic symptoms. Caution is also advised in patients with pre-existing liver dysfunction or co-infection with hepatitis B or C.

Although renal clearance normally accounts for only a small proportion of the dose, maraviroc should be used with caution in patients with renal impairment (creatinine clearance less than 80 mL/minute) who are also taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 as concentrations of maraviroc may be significantly increased. If the impairment is severe (creatinine clearance < 30 mL/minute) patients are at increased risk of orthostatic hypotension, which may lead to further cardiovascular adverse effects; US licensed product information therefore advises that maraviroc may only be considered for use in such cases if they are not also receiving potent inhibitors or inducers of these cytochromes, and where no alternative treatment options exist.

Due to its mechanism of action, maraviroc may impair the immune response to infections and possibly lead to an increased risk of malignancy.

Interactions

Maraviroc is a substrate for the cytochrome P450 isoenzyme CYP3A4 and for P-glycoprotein, and may therefore have several clinically significant interactions. Inhibitors of CYP3A4, such as HIV-protease inhibitors (other than tipranavir), increase the serum concentration of maraviroc. Inducers of CYP3A4 such as efavirenz may decrease serum maraviroc concentrations. No clinically significant interaction is expected between maraviroc and NRTIs, nevirapine, or boosted fosamprenavir or tipranavir.

Non-antiretroviral medications that significantly alter maraviroc metabolism include the CYP3A4 inhibitors ketoconazole, itraconazole, clarithromycin, and nefazodone and the CYP3A4 inducers rifampicin and St John's wort. Maraviroc does not appear to cause clinically significant changes in concentrations of other medications.

Antiviral Action

Maraviroc is an antagonist of the CCR5 chemokine receptor. During infection, HIV binds to the CD4 receptor on the surface of host cells, and then interacts with one of two co-receptors, CCR5 or CXCR4, to allow cell membrane fusion and entry to the cell. By binding to CCR5, maraviroc inhibits this process and prevents strains of HIV-1 that use CCR5 (CCR5-tropic viruses), which appear to be more common in early infection, from entering the cell. It is not active against CXCR4-tropic strains or those with dual or mixed tropism.

Pharmacokinetics

Maraviroc is absorbed after oral doses and peak concentrations occur in 0.5 to 4 hours. There is considerable interindividual variation in the pharmacokinetics. It is 76% bound to plasma proteins. Maraviroc is metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to inactive metabolites. It is excreted in both urine (20%) and faeces (76%) as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Celsentri; *Austral.*: Celsentri; *Austria*: Celsentri; *Belg.*: Celsentri; *Braz.*: Celsentri; *Canad.*: Celsentri; *Chile*: Celsentri; *China*: Celsentri (selsentri); *Cz.*: Celsentri; *Denm.*: Celsentri; *Fr.*: Celsentri; *Ger.*: Celsentri; *Gr.*: Celsentri; *Hong Kong*: Celsentri; *Hung.*: Celsentri; *Irl.*: Celsentri; *Israel*: Celsentri; *Ital.*: Celsentri; *Neth.*: Celsentri; *Norw.*: Celsentri; *Pol.*: Celsentri; *Port.*: Celsentri; *Spain*: Celsentri; *Swed.*: Celsentri; *Switz.*: Celsentri; *Thai.*: Celsentri; *UK*: Celsentri; *USA*: Selzentry.

Moroxydine *(BAN, rINN)*

Moroksidilini; Moroxidin; Moroxidina; Moroxydinum; Мороксидин.

$C_6H_{13}N_5O$=171.2

CAS — 3731-59-7.

ATC — J05AX01.

ATC Vet — QJ05AX01.

UNII — O611591WAH.

Moroxydine Hydrochloride *(BANM, rINNM)*

Abitilguanide Hydrochloride; ABOB; Hidrocloruro de moroxidina; Moroxidina, hidrocloruro de; Moroxydine, Chlorhydrate de; Moroxydini Hydrochloridum; Мороксидина Гидрохлорид.

1-(Morpholinoformimidoyl)guanidine hydrochloride.

$C_6H_{13}N_5O,HCl$=207.7.

CAS — 3160-91-6.

ATC — J05AX01.

ATC Vet — QJ05AX01.

Profile

Moroxydine hydrochloride has been given orally in the treatment of herpes simplex and varicella-zoster infections. It has also been used topically. It is included as an ingredient in preparations for the treatment of cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Virulex Forte; *Mex.*: Amgrip†; Singril; Singril; Singrilen; *S.Afr.*: Corenza C.

Nelfinavir Mesilate *(BANM, rINNM)*

AG-1343 (nelfinavir or nelfinavir mesilate); Mesilato de nelfinavir; Nelfinavir, Mésilate de; Nelfinavir, mesilato de; Nelfinavir Mesylate (USAN); Nelfinavir Mesylate; Nelfinaviri Mesilas; Нелфинавира Мезилат.

3S[2(2S*,3S*),3α,4aβ,8aβ]-*N*-(1,1-Dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinolinecarboxamide monomethanesulphonate; (3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyldecahydro-2-[(2*R*,3*R*)-3-(3-hydroxy-o-toluamido)-2-hydroxy-4-(phenylthio)butyl]isoquinoline-3-carboxamide monomethanesulphonate.

$C_{32}H_{45}N_3O_4S,CH_4O_3S$=663.9

CAS — 159989-64-7 (nelfinavir); 159989-65-8 (nelfinavir mesilate).

ATC — J05AE04.

ATC Vet — QJ05AE04.

UNII — 98D603VP8V.

NOTE. Nelfinavir should not be confused with nevirapine (p. 1005.1).

Pharmacopoeias. In *Int.*

Uses and Administration

Nelfinavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when nelfinavir is used alone, and it is therefore used with other antiretrovirals.

Nelfinavir is given orally as the mesilate, but doses are expressed in terms of the base. Nelfinavir mesilate 292 mg is equivalent to about 250 mg of nelfinavir. Nelfinavir is available as tablets and oral powder. The oral powder should not be taken with acidic foods or drinks as this may result in a bitter taste. Nelfinavir is given in an adult dose of 1.25 g twice daily or 750 mg three times daily with food.

For details of doses in children, see below.

Reviews.

1. Pal VB, Nahata MC. Nelfinavir mesylate: a protease inhibitor. *Ann Pharmacother* 1999; 33: 325–39.
2. Perry CM, *et al.* Nelfinavir: a review of its use in the management of HIV infection. *Drugs* 2005; 65: 2209–44.
3. Olmo M, Podzamczer D. A review of nelfinavir for the treatment of HIV infection. *Expert Opin Drug Metab Toxicol* 2006; 2: 285–300.
4. Brüning A, *et al.* New prospects for nelfinavir in non-HIV-related diseases. *Curr Mol Pharmacol* 2010; 3: 91–7.

Administration in children. For the treatment of HIV infection in children nelfinavir is given orally with other antiretroviral drugs. US licensed product information permits the use of nelfinavir in children 2 years of age and older; the recommended dose is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily with food.

Malignant neoplasms. There has been some interest[1-3] in the potential of nelfinavir as an antineoplastic.

1. Gills JJ, *et al.* Nelfinavir, a new anti-cancer drug with pleiotropic effects and many paths to autophagy. *Autophagy* 2008; 4: 107–9.
2. Brunner TB, *et al.* Phase I trial of the human immunodeficiency virus protease inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer. *J Clin Oncol* 2008; 26: 2699–706.
3. Wu W, *et al.* Nelfinavir: a magic bullet to annihilate cancer cells? *Cancer Biol Ther* 2009; 8: 233–5.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing nelfinavir are diarrhoea, flatulence, nausea, and rash. Raised liver enzymes and decreases in white blood cell counts have also been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including nelfinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including nelfinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Contamination. In June 2007, high levels of ethyl mesilate (ethyl methanesulfonate; EMS) were detected in European-made nelfinavir (*Viracept; Roche*). EMS may cause cancer in humans and has caused birth defects and cancer in *animals*. Nelfinavir was subsequently recalled from the European market in August 2007.[1] The manufacturer later identified and rectified the source of contamination and in September 2007 the EMEA recommended the lifting of the drug's suspension.[2] It was later determined that the exposure to EMS caused by the contaminated product were well below the threshold required for DNA damage to occur.[3] The US manufacturer (*Pfizer, USA*) notified doctors in September 2007 that EMS had been detected in nelfinavir manufactured in the USA but in much lower amounts than in European-made nelfinavir.[4] At the time the FDA considered the risk of stopping nelfinavir therapy resulting from a drug recall to be greater than the risk of taking US-made nelfinavir, but issued recommendations restricting its use specifically in children and pregnant women. However, as of March 31, 2008, all nelfinavir manufactured in the US by Pfizer meets new EMS limits established by the FDA for all patient populations, and these recommendations no longer apply.[5]

1. EMEA. European Medicines Agency agrees on action plan following the recall of Viracept and recommends suspension of the marketing authorisation (issued 21st June, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014204.pdf (accessed 18/08/10)
2. EMEA. European medicines agency recommends lifting of suspension for Viracept (issued 20th September, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014100.pdf (accessed 18/08/10)
3. EMEA. Studies assessed by the EMEA indicate no increased risk of developing cancer for patients who have taken Viracept contaminated with ethyl mesilate (issued 24th July, 2008). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Viracept/38225608en.pdf (accessed 19/10/09)
4. Pfizer, USA. Viracept (nelfinavir mesylate) 250 mg, 625 mg tablets, and powder for oral suspension: important information for prescribers (issued 10th September, 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM154880.pdf (accessed 18/08/10)
5. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Precautions

Nelfinavir should be used with caution, and liver enzyme values monitored, in patients with moderate liver disease; in the USA, the use of nelfinavir in patients with moderate or severe liver disease is not advised. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

For cautions concerning use in children and in pregnancy see under Contamination, above

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nelfinavir as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Nelfinavir is reported to be metabolised in part by cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that induce these isoenzymes may reduce the plasma concentration of nelfinavir. Conversely, when nelfinavir is given with drugs that inhibit CYP3A4 plasma concentrations, nelfinavir concentrations may be increased. It may also alter the pharmacokinetics of drugs metabolised by this isoenzyme system and possibly cause serious adverse effects.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of nelfinavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include

- the alpha$_1$-adrenoceptor antagonist alfuzosin
- antiarrhythmics (amiodarone and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal motility agents (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

Owing to the potential for increased serum concentrations of sildenafil, nelfinavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, nelfinavir may increase serum concentrations of inhaled salmeterol and the combination is not recommended. Omeprazole, rifampicin, and St John's wort decrease the concentration of nelfinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Nelfinavir is a selective, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Mechanisms of resistance to nelfinavir may differ sufficiently from those to other HIV-protease inhibitors to reduce the occurrence of cross-resistance between nelfinavir and other HIV-protease inhibitors. Cross-resistance between nelfinavir and NNRTIs is unlikely because they target different enzymes.

Pharmacokinetics

Nelfinavir is absorbed from the gastrointestinal tract and peak plasma concentrations occur in 2 to 4 hours. Absorption is enhanced when given with food. Nelfinavir is extensively bound to plasma proteins (more than 98%). It is metabolised by oxidation by cytochrome P450 isoenzymes including CYP3A4 and CYP2C19. The major oxidative metabolite has *in-vitro* antiviral activity equal to that of nelfinavir. In patients 13 years of age and older the plasma terminal half-life is 3.5 to 5 hours; in children 2 to 13 years of age, clearance is two to three times greater than in adults. Nelfinavir is excreted mainly in the faeces both as

unchanged drug (22%) and as metabolites (78%). Only about 1 to 2% is excreted in the urine, mainly as unchanged drug.

References.
1. Panhard X, *et al.* Population pharmacokinetic analysis for nelfinavir and its metabolite M8 in virologically controlled HIV-infected patients on HAART. *Br J Clin Pharmacol* 2005; 60: 390–403.
2. Goujard C, *et al.* High variability of indinavir and nelfinavir pharmacokinetics in HIV-infected patients with a sustained virological response on highly active antiretroviral therapy. *Clin Pharmacokinet* 2005; 44: 1267–78.
3. Regazzi M, *et al.* Clinical pharmacokinetics of nelfinavir and its metabolite M8 in human immunodeficiency virus (HIV)-positive and HIV-hepatitis C virus-coinfected subjects. *Antimicrob Agents Chemother* 2005; 49: 643–9.
4. Damle B, *et al.* Pharmacokinetics of nelfinavir in subjects with hepatic impairment. *J Clin Pharmacol* 2006; 46: 1241–9.
5. Fletcher CV, *et al.* Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther* 2008; 83: 300–6.
6. Hirt D, *et al.* Pharmacokinetic modelling of the placental transfer of nelfinavir and its M8 metabolite: a population study using 75 maternal-cord plasma samples. *Br J Clin Pharmacol* 2007; 64: 634–44.
7. Hirt D, *et al.* Effect of CYP2C19 polymorphism on nelfinavir to M8 biotransformation in HIV patients. *Br J Clin Pharmacol* 2008; 65: 548–57.
8. Read JS, *et al.* Pharmacokinetics of new 625 mg nelfinavir formulation during pregnancy and postpartum. *HIV Med* 2008; 9: 875–82.
9. Damle BD, *et al.* Influence of CYP2C19 polymorphism on the pharmacokinetics of nelfinavir and its active metabolite. *Br J Clin Pharmacol* 2009; 68: 682–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Filosfil; Nalvir; Nelfilea; Nemacina; Retroinhi; *Austral.*: Viracept†; *Austria*: Viracept†; *Belg.*: Viracept†; *Braz.*: Viracept; *Canad.*: Viracept; *Chile*: Viracept†; *China*: Viracept (泛罗素); *Cz.*: Viracept†; *Fr.*: Viracept†; *Ger.*: Viracept†; *Gr.*: Viracept†; *Hong Kong*: Viracept; *Hung.*: Viracept†; *India*: Emnel; Neivex; Nel; Nelvir; *Irl.*: Viracept†; *Israel*: Viracept†; *Ital.*: Viracept†; *Jpn*: Viracept; *Malaysia*: Viracept; *Mex.*: Viracept†; *Neth.*: Viracept†; *NZ*: Viracept†; *Philipp.*: Viracept†; *Pol.*: Viracept†; *Port.*: Viracept†; *Rus.*: Viracept (Вирасепт); *S.Afr.*: Viracept; *Singapore*: Viracept; *Spain*: Viracept†; *Switz.*: Viracept†; *Thai.*: Nafavir; Viracept†; *UK*: Viracept†; *Ukr.*: Viracept (Вирасепт)†; *USA*: Viracept; *Venez.*: Nelvir; Viracept.

Nevirapine *(BAN, USAN, rINN)*

BIRG-0587; BI-RG-587; Nevirapiini; Nevirapiini, vedetön; Nevirapin; Nevirapin bezvodý; Nevirapin, vattenfritt; Nevirapina; Névirapine; Névirapine anhydre; Nevirapinum; Nevirapinum Anhydricum; Newirapina bezwodna; Невирапин.

11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*]-[1,4]diazepin-6-one.

$C_{15}H_{14}N_4O$=266.3

CAS — 129618-40-2.

ATC — J05AG01.

ATC Vet — QJ05AG01.

UNII — 99DK7FVK1H.

NOTE. Nevirapine should not be confused with nelfinavir (p. 1004.1).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Eur. permits anhydrous or the hemihydrate.

Ph. Eur. 8: (Nevirapine, Anhydrous). A white or almost white powder. Practically insoluble in water; sparingly soluble or slightly soluble in dichloromethane; slightly soluble in methyl alcohol.

Ph. Eur. 8: (Nevirapine Hemihydrate). A white or almost white powder. Practically insoluble in water; slightly soluble in dichloromethane and in methyl alcohol.

USP 36: (Nevirapine). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white, odourless to nearly odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. The hydrous form is also slightly insoluble in propylene glycol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when nevirapine is used alone, and it is therefore used with other antiretrovirals.

Nevirapine is given orally in an adult dose of 200 mg once daily for the first 14 days, then increased to 200 mg twice daily provided that no rash is present (but see Precautions, below).

If treatment is interrupted for more than 7 days, it should be reintroduced using the lower dose for the first 14 days as for new treatment.

For details of doses in infants, children, and adolescents, see below.

Nevirapine is often used in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection. In women in whom HAART is not indicated, or where it is not available, a single oral dose of nevirapine 200 mg may be given at the onset of labour, with a course of zidovudine and lamivudine, for perinatal cover (see HIV Infection Prophylaxis, p. 959.1).

References.
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2. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs* 2000; 2: 373–407.
3. Dorenbaum A, *et al.* Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* 2002; 288: 189–98.
4. Moodley D, *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; 187: 725–35.
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6. Tailemant M, *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; 351: 217–28.
7. Shapiro RL, *et al.* Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS* 2006; 20: 1281–8.
8. Lockman S, *et al.* Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007; 356: 135–47.
9. Parienti JJ, *et al.* SIROCCO study team. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. *Clin Infect Dis* 2007; 45: 263–6.
10. Dart Trial Team. Twenty-four-week safety and tolerability of nevirapine vs. abacavir in combination with zidovudine/lamivudine as first-line antiretroviral therapy: a randomized double-blind trial (NORA). *Trop Med Int Health* 2008; 13: 6–16.
11. Ena J, *et al.* Switching from suppressive protease inhibitor-based regimens to nevirapine-based regimens: a meta-analysis of randomized controlled trials. *HIV Med* 2008; 9: 747–56.
12. Rodríguez-Arrondo F, *et al.* Long-term effectiveness and safety outcomes in HIV-1-infected patients after a median time of 6 years on nevirapine. *Curr HIV Res* 2009; 7: 526–32.
13. Calmy A, *et al.* HAART Observational Medical Evaluation and Research Cohort. Netherlands ATHENA Observational Cohort. Safety and efficacy of once-daily nevirapine dosing: a multicohort study. *Antivir Ther* 2009; 14: 931–8.
14. Reliquet V, *et al.* Twelve-year experience of nevirapine use: benefits and convenience for long-term management in a French cohort of HIV-1-infected patients. *HIV Clin Trials* 2010; 11: 110–17.
15. Coovadia A, *et al.* Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA* 2010; 304: 1082–90.
16. Mbuagbaw LCE, *et al.* Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naive individuals. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 25/02/11).

Administration in children. For the treatment of HIV infection in infants, children, and adolescents nevirapine is given orally with other antiretroviral drugs. The following doses by body-weight have been suggested according to age:

- from 15 days to 8 years: 4 mg/kg once daily for 14 days and then, if no rash is present, 7 mg/kg twice daily
- 8 to 16 years: 4 mg/kg once daily for 14 days then 4 mg/kg twice daily thereafter

Alternatively, the dose may be calculated according to body-surface: an oral dose of 150 mg/m^2 once daily for two weeks is given followed by 150 mg/m^2 twice daily thereafter if no rash is present. A total dose of 400 mg daily should not be exceeded. The *BNFC* suggests higher doses of 150 to 200 mg/m^2 once daily for two weeks and 150 to 200 mg/m^2 twice daily thereafter if no rash is present also with a daily maximum of 400 mg.

For information on the use of nevirapine in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection see HIV Infection Prophylaxis, p. 959.1.

Administration in renal impairment. Dose adjustments are not required for patients with a creatinine clearance more than 20 mL/min. Patients on dialysis should receive an additional 200 mg of nevirapine after each dialysis session.

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing nevirapine is rash (usually mild to moderate, maculopapular, erythematous, and sometimes pruritic), generally occurring within 6 weeks of starting therapy. Severe and life-threatening skin reactions (with some fatalities) have occurred, including Stevens-Johnson syndrome and, more rarely, toxic epidermal necrolysis. Hypersensitivity reactions including angioedema, urticaria, and anaphylaxis have been reported. Rashes may occur alone or in the context of hypersensitivity reactions when they may be accompanied by other symptoms such as fever, arthralgia, myalgia, lymphadenopathy, eosinophilia, granulocytopenia, or renal dysfunction. Granulocytopenia occurs more commonly in children than in adults. Severe hepatotoxicity, including hepatitis and hepatic necrosis, occasionally fatal, has occurred and may be more prevalent in women and patients with high CD4+ counts at the start of treatment. Serious hepatotoxicity has also been reported in HIV-uninfected persons taking multiple doses of nevirapine for HIV postexposure-prophylaxis. Rhabdomyolysis has occurred in patients with skin and/or liver reactions. Other common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, fatigue, drowsiness, fever, myalgia, and headache.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including nevirapine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including nevirapine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the liver. The FDA has noted[1] that symptomatic liver toxicity is more frequent with nevirapine than with other antiretrovirals. Toxicity consists of elevated liver enzyme values plus at least one other symptom such as rash, flu-like symptoms, or fever, and may progress to rapidly occurring liver failure despite monitoring. It typically occurs after a few weeks of dosing, and women and patients with higher CD4+ counts are at greater risk. Deaths have occurred, including some in pregnant women (see also Pregnancy, p. 1006.1), but serious toxicity has not been reported after single doses or in HIV-infected children.

Further references.[2-7]

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3. CSM/MCA. Nevirapine (Viramune): serious adverse reactions when used in HIV post exposure prophylaxis. *Current Problems* 2001; 27: 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074566&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
4. Gonzalez de Requena D, *et al.* Liver toxicity caused by nevirapine. *AIDS* 2002; 16: 290–1.
5. De Maat MM, *et al.* Hepatotoxicity following nevirapine-containing regimens in HIV-1-infected individuals. *Pharmacol Res* 2002; 46: 295–300.
6. Patel SM, *et al.* Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J Acquir Immune Defic Syndr* 2004; 35: 120–5.
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Effects on the skin. References.
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2. Wetterwald E, *et al.* Nevirapine-induced overlap Stevens-Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 1999; 140: 980–2.
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4. Antinori A, *et al.* Female sex and the use of anti-allergic agents increase the risk of developing cutaneous rash associated with nevirapine therapy. *AIDS* 2001; 15: 1579–81.
5. de Maat MM, *et al.* Incidence and risk factors for nevirapine-associated rash. *Eur J Clin Pharmacol* 2003; 59: 457–62.
6. Manosuthi W, *et al.* Incidence and risk factors of nevirapine-associated skin rashes among HIV-infected patients with CD4 cell counts <250 cells/microL. *Int J STD AIDS* 2007; 18: 782–6.
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8. Kiertiburanakul S, *et al.* Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. *Curr HIV Res* 2008; 6: 65–9.
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Precautions

Patients taking nevirapine should be closely monitored for adverse skin reactions and hepatotoxicity during the first 18 weeks of treatment; extra vigilance is advised during the first 6 weeks of treatment. Nevirapine should be used with extreme caution in patients with moderate hepatic impairment (Child-Pugh class B); it is contra-indicated in those with severe hepatic impairment (Child-Pugh class C). Patients with high CD4+ counts (greater than 250 cells/microlitre in women or 400 cells/microlitre in men), particularly those with a detectable viral load, are at increased risk for hepatotoxicity; nevirapine should not be

started in these patients unless the benefit clearly outweighs the risk. Patients with elevated transaminase levels at the start of nevirapine therapy, and those who are co-infected with chronic hepatitis B or C are also at a higher risk of hepatotoxicity. The UK licensed product information suggests that liver function should be monitored every 2 weeks during the first 2 months of treatment, again at 3 months, and then regularly thereafter.

Treatment should be permanently stopped in patients who suffer a severe rash, rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise), hypersensitivity reactions, or clinical hepatitis. Transaminase levels should be checked for all patients who develop a rash in the first 18 weeks of treatment and nevirapine should be temporarily stopped if liver enzyme levels increase to greater than 5 times the upper limit of normal or the patient has symptoms suggestive of hepatitis. In some patients treatment may be restarted at the initial dose if liver function returns to baseline values and the patient has no clinical symptoms of hepatitis or signs of a rash (although permanent stoppage is necessary if abnormalities recur). In some cases hepatic injury progresses despite stopping the drug. Dose escalation should not be attempted in patients developing any rash during the first 14 days of treatment until the rash has resolved, however, if dose escalation is not possible within 28 days of starting therapy an alternative regimen should be sought. Patients or their carers should be counselled on how to recognise hypersensitivity reactions and instructed to seek immediate medical attention if they occur. Doses may need to be modified in patients on renal dialysis.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nevirapine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Nevirapine has not been associated with teratogenicity in *animals* Licensed product information states that the Antiretroviral Pregnancy Registry has not found an increased risk of birth defects after first trimester exposures to nevirapine and the prevalence of birth defects after exposure in any trimester was comparable to the prevalence in the general population.

Significant and potentially life-threatening maternal toxicity may occur in women using nevirapine-containing treatment regimens, particularly when nevirapine is used for the first time,[1] although others[2] have not found the risk of hepatotoxicity in pregnant women given nevirapine-based regimens to be any greater than with other antiretrovirals. Due to the risk of severe hepatotoxicity, US guidelines for use of antiretroviral drugs in pregnant HIV-infected women[3] advise against starting nevirapine in pregnant women with CD4+ counts greater than 250 cells/microlitre unless the benefit clearly outweighs the risk; women who become pregnant while on a well-tolerated nevirapine-containing regimen may continue therapy, regardless of CD4+ count.

1. van Schalkwyk JE, *et al.* Serious toxicity associated with continuous nevirapine-based HAART in pregnancy. *BJOG* 2008; 115: 1297–302.
2. Ouyang DW, *et al.* Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS* 2010; 24: 109–14.
3. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)

Interactions

Nevirapine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6. Consequently it may compete with other drugs metabolised by this system, possibly resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of nevirapine; nevirapine itself acts as a mild to moderate enzyme inducer and may thus reduce plasma concentrations of other drugs.

Rifampicin and St John's wort decrease the concentration of nevirapine; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Antivirals. For the effect of nevirapine on *HIV-protease inhibitors*, see p. 988.1.

Opioids. Nevirapine may induce the metabolism of *methadone* (p. 91.1) resulting in reduced plasma-methadone concentrations.

Antiviral Action

Nevirapine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to nevirapine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Nevirapine is readily absorbed after oral doses and absorption is not affected by food or antacids. Bioavailability is greater than 90%. Nevirapine tablets and oral suspension are comparably bioavailable and interchangeable at doses up to 200 mg. Peak plasma concentrations occur 4 hours after a single dose. Nevirapine is about 60% bound to plasma proteins. Concentrations in the CSF are about 45% of those in plasma. Nevirapine crosses the placenta and is distributed into breast milk. It is extensively metabolised by hepatic microsomal enzymes, mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, to several hydroxylated metabolites. Autoinduction of these enzymes results in a 1.5- to 2-fold increase in apparent oral clearance after 2 to 4 weeks at usual dosage, and a decrease in terminal half-life from 45 hours to 25 to 30 hours over the same period. Nevirapine is mainly excreted in the urine as glucuronide conjugates of the hydroxylated metabolites.

In children, nevirapine elimination accelerates during the first years of life, reaching a maximum at around 2 years of age, followed by a gradual decline during the rest of childhood; values in children under 8 years are about twice those in adults.

References.

1. Mirochnick M, *et al.* Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet* 2000; 39: 281–93.
2. Almond LM, *et al.* Intracellular and plasma pharmacokinetics of nevirapine in human immunodeficiency virus-infected individuals. *Clin Pharmacol Ther* 2005; 78: 132–42.
3. von Hentig N, *et al.* A comparison of the steady-state pharmacokinetics of nevirapine in men, nonpregnant women and women in late pregnancy. *Br J Clin Pharmacol* 2006; 62: 552–9.
4. Cammett AM, *et al.* Pharmacokinetic assessment of nevirapine and metabolites in human immunodeficiency virus type 1-infected patients with hepatic fibrosis. *Antimicrob Agents Chemother* 2009; 53: 4147–52.
5. Benaboud S, *et al.* Population pharmacokinetics of nevirapine in HIV-1-infected pregnant women and their neonates. *Antimicrob Agents Chemother* 2011; 55: 331–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Filide; Nerapin; Protease; Ritvir; Virainhi; Viramune; *Austral.*: Viramune; *Austria*: Viramune; *Belg.*: Viramune; *Braz.*: Neviral; Viramune; *Canad.*: Viramune; *Chile*: Viramune; *China*: Ai Ji (艾极); Ai Tai (艾太); Ai Wei Ning (艾韦宁); Li Wei Er (立维尔); Nuo Lan Pin (诺兰频); Viramune (维乐命); Wei Le Si (伟乐司); *Cz.*: Viramune; *Denm.*: Viramune; *Fin.*: Viramune; *Fr.*: Viramune; *Ger.*: Viramune; *Gr.*: Viramune; *Hong Kong*: Viramune; *Hung.*: Viramune; *India*: Nev; Neve; Nevimune; Nevipan; Nevir; Neviretro; *Indon.*: Viramune†; *Irl.*: Viramune; *Israel*: Viramune; *Ital.*: Viramune; *Jpn*: Viramune; *Malaysia*: Hirapine; Nevipan; Viramune; *Mex.*: Viramune; *Neth.*: Viramune; *Norw.*: Viramune; *NZ*: Viramune; *Pol.*: Viramune; *Port.*: Viramune; *Rus.*: Viramune (Вирамун); *S.Afr.*: Nevivir; Viramune; Viropon; *Singapore*: Viramune; *Spain*: Viramune; *Swed.*: Viramune; *Switz.*: Viramune; *Thai.*: Neravir; Viramune; *Turk.*: Viramune; *UK*: Viramune; *Ukr.*: Viramune (Вирамун); *USA*: Viramune; *Venez.*: Nevimune; Viramune.

Multi-ingredient Preparations. *Arg.*: Lazinevir; *India*: Cytocom-N; Duovir N; Emduo-N; Emtri; Lami Plus; Lamostad-N; Lazid-N; Triomune; *S.Afr.*: Sonke-LamiNevStav; Triomune; Virtrium; *Thai.*: GPO-Vir S; GPO-Vir Z; *Venez.*: Triomune.

Pharmacopoeial Preparations

USP 36: Nevirapine Oral Suspension; Nevirapine Tablets.

Oseltamivir Phosphate

(BANM, USAN, rINNM)

Fosfato de oseltamivir; GS-4104/002; Oseltamivir, fosfato de; Oseltamivir, Phosphate d'; Oseltamivir Phosphas; Ro-64-0796/002; Осельтамивира Фосфат.

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (1:1).

$C_{16}H_{28}N_2O_4.H_3PO_4$=410.4

CAS — 196618-13-0 (oseltamivir); 204255-11-8 (oseltamivir phosphate).

ATC — J05AH02.

ATC Vet — QJ05AH02.

UNII — 4A3O49NGEZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Oseltamivir Phosphate). A white or almost white powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Oseltamivir Phosphate). White to off-white powder. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol, in dimethyl sulfoxide, and in propylene glycol; sparingly soluble in dimethylformamide; very slightly soluble in isopropyl alcohol and in macrogol 400; practically insoluble in acetonitrile, in acetone, in dichloromethane, and in *n*-hexane. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Oseltamivir is a prodrug of oseltamivir carboxylate, an inhibitor of the enzyme neuraminidase (sialidase), which has a role in the infectivity and replication of influenza A and B viruses. It is used for the treatment and postexposure prophylaxis of influenza A and B (p. 1007.1), including pandemic strains.

Oseltamivir is given orally as the phosphate, but doses are expressed in terms of the base. Oseltamivir phosphate 98.5 mg is equivalent to about 75 mg of oseltamivir. For *treatment* a dose of 75 mg is given twice daily for 5 days, beginning as soon as possible (within 48 hours) after the onset of symptoms. For *postexposure prophylaxis* the usual dose is 75 mg given once daily for at least 10 days and for up to 6 weeks during an epidemic; therapy should begin within 48 hours of exposure. In the EU intravenous oseltamivir phosphate is also available for use in patients from 1 year of age on compassionate grounds.

For details of doses in children, see below.

Dosage should be reduced in patients with renal impairment (see p. 1007.1).

Oseltamivir has been tried both for prophylaxis and treatment of H5N1 disease (avian influenza) and has been proposed as a measure to contain any potential pandemic until an effective vaccine could be developed.

Administration. Emergency compounding of an oral suspension from oseltamivir capsules may be necessary during situations when commercially manufactured oral suspension is not readily available. UK licensed product information suggests those who are unable to swallow capsules may be given the appropriate doses of oseltamivir by opening oseltamivir capsules and pouring the contents into a suitable, small amount (1 teaspoon maximum) of sweetened food product to mask the bitter taste. The mixture should be stirred and the entire contents given to the patient immediately after preparation.

Alternatively, licensed product information provides guidelines for a pharmacist to compound a solution (final concentration 15 mg/mL for children more than 1 year of age) from oseltamivir capsules using either water containing 0.1% w/v sodium benzoate, cherry syrup (*Humco*), or *Ora-Sweet SF*, as a vehicle. UK licensed product information also provides guidelines for compounding a 10 mg/mL solution for use in children less than 1 year of age.

Administration in children. Oseltamivir is given orally in the treatment and prophylaxis of influenza A and B in children aged 1 year and over. In addition, during the 2009 H1N1 pandemic, dosing recommendations for oseltamivir for treatment and postexposure prophylaxis in children less than 1 year of age were also developed.

Doses for children 1 year of age and over are determined by body-weight and may be given twice daily for 5 days for treatment, or once daily for 10 days for prophylaxis, of influenza A and B as follows:

- children over 40 kg: 75 mg
- more than 23 kg to 40 kg: 60 mg
- more than 15 kg to 23 kg: 45 mg
- 15 kg or less: 30 mg

Doses for use in children less than 1 year of age are determined by age and body-weight, and are given twice daily for 5 days for treatment, or once daily for 10 days for prophylaxis. The following doses are recommended:

- infants 0 to 1 month of age: 2 mg/kg
- those from 1 to 3 months of age: 2.5 mg/kg
- those from 3 to 12 months of age: 3 mg/kg

In the USA the recommended treatment dose of oseltamivir in children less than 1 year of age is 3 mg/kg twice daily.[1,2] Although it is not licensed for postexposure prophylaxis in children under 1 year of age, the CDC[1] recommends a dose of 3 mg/kg once daily; for those aged less than 3 months prophylaxis is not recommended unless considered to be essential. For the treatment of infants aged 14 days or less WHO recommends a dose of 2.5 to 3 mg/kg once daily and in those aged 15 days to 12 months a dose of 3 mg/kg twice daily.[3] *Premature infants* might have a slower clearance of oseltamivir as a result of an immature renal system and therefore the weight-based dosing recommendations for full-term infants are probably not appropriate, furthermore there are insufficient data to recommend a specific dose for them.[1]

Therapy should begin within 48 hours of exposure or the onset of symptoms. During a community outbreak, prophylaxis may be continued for up to 6 weeks.

The *BNFC* advises the following adjustments of normal doses in children with **renal impairment** according to the estimated glomerular filtration rate (eGFR):

For *treatment of influenza*:
- eGFR > 30 to 60 mL/minute per 1.73m²: 40% of normal dose twice daily
- eGFR > 10 to 30 mL/minute per 1.73m²: 40% of normal dose once daily
- eGFR ≤ 10 mL/minute per 1.73m²: use not recommended

For *prevention of influenza*:
- eGFR > 30 to 60 mL/minute per 1.73m²: 40% of normal dose once daily
- eGFR > 10 to 30 mL/minute per 1.73m²: 40% of normal dose every 48 hours
- eGFR ≤ 10 mL/minute per 1.73m²: use not recommended

1. CDC. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60 (RR-1): 1–24. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf (accessed 16/04/13)
2. American Academy of Pediatrics Committee on Infectious Diseases. Policy statement–recommendations for prevention and control of influenza in children, 2010-2011. *Pediatrics* 2010; 126: 816–26. Also available at: http://pediatrics.aappublications.org/cgi/reprint/126/4/816 (accessed 08/02/11)
3. WHO. WHO Guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses; part 2 review of evidence (issued February 2010). Geneva: WHO, 2010. Available at: http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt_part2.pdf (accessed 16/04/13)

Administration in renal impairment. Oral doses of oseltamivir should be reduced in patients with renal impairment, according to creatinine clearance (CC).

Licensing authorities differ in their recommendations. UK licensed product information gives the following guidance for **adults**:

For *treatment of influenza*:
- CC > 30 to 60 mL/minute: 30 mg twice daily
- CC > 10 to 30 mL/minute: 30 mg once daily
- CC ≤ 10 mL/minute: use not recommended
- haemodialysis patients: 30 mg after each dialysis session
- peritoneal dialysis patients: 30 mg single dose

For *prevention of influenza*:
- CC > 30 to 60 mL/minute: 30 mg once daily
- CC > 10 to 30 mL/minute: 30 mg every second day
- CC ≤ 10 mL/minute: use not recommended
- haemodialysis patients: 30 mg after every second dialysis session
- peritoneal dialysis patients: 30 mg once weekly

US licensed product information advises that the dose of oseltamivir be reduced in adults with CC between 10 and 30 mL/minute; 75 mg daily is recommended for *treatment of influenza*, and 75 mg every other day *or* 30 mg daily is recommended for *prophylaxis of influenza*. No recommendations are given for patients with end-stage renal disease, including those who are dialysis-dependent.

For details of dose adjustments in children with renal impairment, see p. 1006.3.

Influenza. Reviews[1-11] of oseltamivir and other neuraminidase inhibitors in the treatment and prophylaxis of influenza (p. 960.2). There is some evidence[12] that zanamivir is more effective than oseltamivir for influenza B. However, a study[13] in Japanese children found oseltamivir and zanamivir to be equally effective in reducing the febrile period in those with influenza A (H1N1), influenza A (H3N2), and influenza B virus infection. A systematic review and quantitative analysis[14] to evaluate the safety and efficacy of extended-duration (more than 4 weeks) use of neuraminidase inhibitors for prophylaxis against seasonal influenza, reported that there was no statistically significant difference between oseltamivir and zanamivir prophylaxis for preventing symptomatic influenza among immunocompetent white and Japanese adults, although nausea and vomiting were more common among those who took oseltamivir.

1. Gubareva LV, *et al.* Influenza virus neuraminidase inhibitors. *Lancet* 2000; 355: 827–35.
2. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. *Drugs* 2001; 61: 263–83.
3. Matheson NJ, *et al.* Neuraminidase inhibitors for preventing and treating influenza in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
4. Cooper NJ, *et al.* Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003; 326: 1235–9.
5. Dutkowski R, *et al.* Safety and pharmacology of oseltamivir in clinical use. *Drug Safety* 2003; 26: 787–801.
6. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; 55 (suppl 1): i5–i21.
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8. Jefferson T, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 18/08/10).
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10. Widmer N, *et al.* Oseltamivir in seasonal, avian H5N1 and pandemic 2009 A/H1N1 influenza: pharmacokinetic and pharmacodynamic characteristics. *Clin Pharmacokinet* 2010; 49: 741–65.
11. Heinonen S, *et al.* Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. *Clin Infect Dis* 2010; 51: 887–94.
12. Kawai N, *et al.* A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect* 2008; 56: 51–7.
13. Sugaya N, *et al.* Comparison of the clinical effectiveness of oseltamivir and zanamivir against influenza virus infection in children. *Clin Infect Dis* 2008; 47: 339–45.
14. Khazeni N, *et al.* Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. *Ann Intern Med* 2009; 151: 464–73.

Adverse Effects

The most commonly reported adverse effects associated with oseltamivir treatment or prophylaxis in adults are nausea and vomiting, abdominal pain, bronchitis, insomnia, and vertigo. Diarrhoea, dizziness, headache, cough, and fatigue may occur, but many adverse effects may be difficult to distinguish from the symptoms of influenza. Other adverse effects occurring less commonly or for which the frequency of occurrence is unknown have included unstable angina, anaemia, arrhythmias, gastrointestinal bleeding, haemorrhagic or pseudomembranous colitis, pneumonia, pyrexia, and peritonsillar abscess. There have been occasional reports of anaphylaxis and skin rashes, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Elevated liver enzymes and hepatitis, including cases of fatal fulminant hepatitis or hepatic failure, have been reported rarely. Prophylaxis in adults has also been associated with aches and pains, dyspepsia, rhinorrhoea, and upper respiratory-tract infections.

The most commonly reported adverse effects in children receiving treatment or prophylaxis with oseltamivir are vomiting and other gastrointestinal problems. Other commonly occurring adverse events include asthma, bronchitis, conjunctivitis, dermatitis, epistaxis, ear disorders and otitis media, lymphadenopathy, pneumonia, and sinusitis.

There have been postmarketing reports (mainly in Japanese children and adolescents) of neuropsychiatric adverse effects (see below).

Incidence of adverse effects. A cross-sectional online survey[1] reporting on schoolchildren taking prophylactic oseltamivir for the pandemic (H1N1) 2009 influenza found that less than half (48%) of those in primary school completed a full course, compared with about three-quarters (76%) of secondary school pupils. More than half (53%) of all the children reported one or more adverse effects. Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, stomach pain or cramps were reported by 40% of children, while 18% reported a mild neuropsychiatric adverse effect such as poor concentration, inability to think clearly, problems in sleeping, feeling dazed or confused, bad dreams or nightmares, or behaving strangely. Neuropsychiatric adverse effects were more commonly reported by secondary (20%) than primary (13%) schoolchildren.

The MHRA (UK) reported[2] that between 23rd July 2009 and 6th October 2009, 628 351 treatment courses of oseltamivir had been issued (for management of the pandemic (H1N1) 2009 influenza via the National Pandemic Flu Service) and 1365 suspected adverse effects to oseltamivir had been voluntarily submitted to them between 1st April 2009 and 8th October 2009. The most commonly reported suspected adverse effects were consistent with the recognised adverse effects of oseltamivir, such as mild allergic reactions, gastrointestinal effects, headache, and dizziness, all of which can be caused by a flu-like illness; no new safety concerns were identified. However, they also received 6 reports in which the patient died, as well as some reports of liver reactions, including two reports of liver failure, but there is no evidence to confirm that oseltamivir was directly responsible for any of these events.

1. Kitching A, *et al.* Oseltamivir adherence and side effects among children in three London schools affected by influenza A(H1N1)v, May 2009–an internet-based cross-sectional survey. *Eur Surveill* 2009; 14 (30th Jul.) 2–5. Available at: http://www.eurosurveillance.org/images/dynamic/EE/V14N30/art19287.pdf (accessed 22/10/09)
2. MHRA. UK suspected adverse drug reaction (ADR) analysis influenza antivirals - oseltamivir (Tamiflu) and zanamivir (Relenza), (issued 15 October 2009). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con059973.pdf (accessed 22/10/09)

Neuropsychiatric effects. An FDA review of the Adverse Event Reporting System (AERS) database from March 2004 to April 2005 reported 75 cases of serious adverse effects linked to the use of oseltamivir in children; 69 from Japan, 5 from USA, and 1 from Canada. Thirty-two cases of neuropsychiatric adverse effects including cases of delirium, abnormal behaviour, hallucinations, convulsions, and encephalitis, were reported, with 31 of these cases being reported from Japan. Twelve deaths were reported; 4 from sudden death, 4 due to cardiopulmonary arrest, and others due to disturbance of consciousness (without falling), pneumonia, asphyxiation, and acute pancreatitis with cardiopulmonary arrest. All deaths were reported from Japan.[1] The Japanese Ministry of Health Labour and Welfare reported that from 2001 to May 2007 they received 1377 adverse effects reports associated with the use of oseltamivir, including 567 reports of serious neuropsychiatric adverse effects and 211 cases of abnormal behaviour. Death was reported in 71 cases.[2] After the suicides of 2 adolescents, the Japanese authorities advised against the use of oseltamivir in adolescents aged 10 to 19 years.[3] However, given that influenza itself may have neuropsychiatric sequelae, any causal relationship with the drug remains unproven.[1,3]

A manufacturer-initiated comprehensive assessment[4] identified 3051 spontaneous reports of neuropsychiatric adverse effects in influenza patients treated with oseltamivir between 1999 and 15 September 2007; 2772 (90.9%) events were from Japan, 190 (6.2%) from the USA, and 89 (2.9%) from other countries. During this period oseltamivir was prescribed to around 48 million people worldwide. Neuropsychiatric adverse effects were more common in children (2218 events in 1808 children aged 16 years and younger versus 833 events in 658 adults) and more frequently reported in males. They generally occurred within 48 hours of starting treatment and the onset of influenza illness, with the most commonly reported neuropsychiatric adverse effects being abnormal behaviour, delusions, perceptual disturbances, and delirium or delirium-like events. Most of the reported neuropsychiatric adverse effects resolved spontaneously, but in rare cases resulted in injury or death. The available data indicated that the incidence of neuropsychiatric adverse effects in those who took oseltamivir was not higher than in those who did not. Furthermore, no clinically relevant differences in plasma pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate were noted between Japanese and Caucasian patients.

See also Incidence of Adverse Effects, above

1. FDA, Center for Drug Evaluation and Research. Pediatric safety update for Tamiflu: Pediatric Advisory Committee meeting (issued 18 November 2005). Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_06_06_summary.pdf (accessed 13/06/08)
2. Hama R. Oseltamivir's adverse reactions: Fifty sudden deaths may be related to central suppression. *BMJ* 2007; 335: 59.
3. Maxwell SRJ. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007; 334: 1232–3.
4. Toovey S, *et al.* Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Safety* 2008; 31: 1097–114.

Precautions

Oseltamivir is not recommended in patients with creatinine clearance of 10 mL/minute or less and it should be given with caution and dosage should be reduced in patients with a creatinine clearance of 10 to 30 mL/minute.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Breast feeding. Oseltamivir and its active metabolite are distributed into breast milk in *rodents*. Licensed product information recommends that it should only be given to breast-feeding mothers if the potential benefit justifies the potential risk.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oseltamivir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Studies in *rodents* given high doses of oseltamivir have not found it to be fetotoxic or embryotoxic. Data on the use of oseltamivir in pregnant women are limited and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk; prescribing guidance from local health authorities should also be taken into consideration.

Pregnant women with influenza have an increased risk of morbidity, particularly due to respiratory complications, and high excess mortality rates have been seen in previous influenza pandemics.[1] Healthcare authorities[2,3] therefore supported the use of a neuramidase inhibitor such as oseltamivir in pregnant women during the pandemic (H1N1) 2009 influenza virus outbreak.

Reviews[4-6] of medical records for pregnant women treated with a neuramidase inhibitor during the 2009 influenza pandemic indicated that treatment within 48

hours of onset of symptoms was associated with better outcomes.[5] A review[1] of the use of oseltamivir in pregnancy reported that adverse pregnancy outcomes were not found to be higher than background incidence rates, and that oseltamivir did not appear to be causally related to adverse pregnancy or fetal outcomes.

1. Donner B, *et al.* Safety of oseltamivir in pregnancy: a review of preclinical and clinical data. *Drug Safety* 2010; 33: 631–42.
2. CDC. Updated interim recommendations for obstetric health care providers related to use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available at: http://www.cdc.gov/H1N1flu/pregnancy/antiviral_messages.htm (accessed 22/05/13)
3. WHO. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance (issued November 2009). Available at: http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf (accessed 22/05/13)
4. Louie JK, *et al.* Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010; 362: 27–35.
5. Siston AM, *et al.* Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA* 2010; 303: 1517–25.
6. CDC. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)—United States, April 2009–August 2010. *MMWR* 2011; 60: 1193–6.

Interactions

Oseltamivir may potentially inhibit replication of the influenza virus in live influenza virus vaccines. Therefore, US licensed product information states that live influenza virus vaccines should not be given until 48 hours after stopping oseltamivir and that oseltamivir should not be given for 2 weeks after live influenza virus vaccines have been given. Inactivated (split virion or surface antigen) vaccines are not expected to be affected by oseltamivir.

Antiviral Action

Oseltamivir has antiviral activity similar to that of zanamivir (p. 1024.2). Its active metabolite, oseltamivir carboxylate, selectively blocks the viral surface enzyme neuraminidase, thereby preventing the release of virus particles from infected cells. Oseltamivir is active against influenza A and B viral neuraminidase.

Resistance. Oseltamivir-resistant type A virus, including H5N1 subtypes, have been reported in patients being treated for influenza.[1-3] A study[1] in Japan found that 9 of 50 (18%) children with influenza A (H3N2) virus infection who had been treated with oseltamivir had a virus with a drug-resistance mutation in the neuraminidase gene (mainly R292K). Another study[4] in Japan reported resistant influenza A (H1N1) viruses with the H274Y mutation in 7 of 43 (16%) oseltamivir-treated children. In both these studies the children were given an oral dose of 2 mg/kg twice daily. However, a larger study[5] in the US reported no resistance in children who received age- and weight-tailored (and therefore sometimes substantially higher) doses than those used in the Japanese studies. A small study[6] in the UK, during the 2005-2007 influenza season, in children treated with a tiered weight-based oseltamivir dosing regimen recovered antiviral resistant viruses from 3 of 11 children with influenza A (H1N1), 1 of 34 with influenza A (H3N2), and from none of the 19 children with influenza B virus. Transmission of oseltamivir-resistant influenza was not very common during the 2006-2007 influenza season, but by the winter of 2007-2008 H274Y mutations were frequently identified among influenza A (H1N1) isolates in many areas of Europe[7,8] and in December 2008 the CDC reported that 24 out of 25 influenza A (H1N1) isolates tested were resistant to oseltamivir but remained susceptible to zanamivir.[9] A study[10] in the USA reported that 98.5% of 268 influenza A (H1N1) isolates from the 2008 to 2009 season were resistant to oseltamivir and that they carried the neuraminidase H274Y mutation. Other N1-containing strains, including avian influenza A (H5N1), which have the same H274Y mutation are therefore also likely to develop oseltamivir resistance during treatment, but not zanamivir resistance.[7,8] Influenza A (H3N2) remains susceptible to both oseltamivir and zanamivir.[7]

Systematic surveillance conducted during the 2009 (H1N1) influenza pandemic, by the Global Influenza Surveillance Network has detected sporadic and infrequent incidents of oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, but there is no evidence of person-to-person transmission or that these resistant viruses are circulating within communities or worldwide. As of the 25th September 2009, 28 resistant viruses had been detected and characterised worldwide. All of these viruses had the same H275Y mutation that confers resistance to oseltamivir, but not to zanamivir. Twelve of these drug-resistant viruses were associated with the use of oseltamivir for postexposure prophylaxis, and 10 were isolated from patients receiving oseltamivir treatment, 6 of whom had severe immunosuppression; 2 were isolated from patients who were not taking oseltamivir for either treatment or prophylaxis.[11]

Resistance to influenza B virus does not occur as often as to influenza A viruses. A study[12] in 74 Japanese children infected with influenza B virus and given oseltamivir reported 1 case of reduced sensitivity to neuraminidase inhibitors; reduced sensitivity was also identified in 7 of 422 viruses from untreated patients, indicating that resistant influenza B viruses appear to be transmitted within communities and families.

No viruses resistant to zanamivir have been isolated from immunocompetent people,[13] although resistance occurred in an immunocompromised child infected with influenza B.[14]

1. Kiso M, *et al.* Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004; 364: 759–65.
2. de Jong MD, *et al.* Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; 353: 2667–72.
3. Le QM, *et al.* Avian flu: isolation of drug-resistant H5N1 virus. *Nature* 2005; 437: 1108. Correction. *ibid.*; 438: 754.
4. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; 55 (suppl 1): i5–i21.
5. Hayden FG, *et al.* Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004; 189: 440–9.
6. Stephenson I, *et al.* Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis* 2009; 48: 389–96.
7. Monto AS. Implications of antiviral resistance of influenza viruses. *Clin Infect Dis* 2009; 48: 397–9.
8. Weinstock DM, Zuccotti G. The evolution of influenza resistance and treatment. *JAMA* 2009; 301: 1066–9.
9. CDC. Update: Influenza Activity—United States, September 28–November 29, 2008. *MMWR* 2008; 57: 1329–32. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5749.pdf (accessed 26/10/09)
10. Dharan NJ, *et al.* Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA* 2009; 301: 1034–41.
11. WHO. Antiviral use and the risk of drug resistance pandemic (H1N1) 2009 briefing note 12 (issued 25th September 2009). Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_antiviral_use_20090925/en/index.html (accessed 19/10/09)
12. Hatakeyama S, *et al.* Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. *JAMA* 2007; 297: 1435–42.
13. Moscona A. Oseltamivir-resistant influenza? *Lancet* 2004; 364: 733–4.
14. Gubareva LV, *et al.* Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998; 178: 1257–62.

Pharmacokinetics

Oseltamivir is readily absorbed from the gastrointestinal tract after oral doses and is extensively metabolised in the liver to the active entity, oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as the carboxylate. Binding to plasma proteins is about 3% for the carboxylate and 42% for the parent drug. Oseltamivir has a plasma half-life of 1 to 3 hours and the carboxylate a plasma half-life of 6 to 10 hours. The carboxylate is not metabolised further and is eliminated in the urine.

Reviews.

1. Abe M, *et al.* Pharmacokinetics of oseltamivir in young and very elderly subjects. *Ann Pharmacother* 2006; 40: 1724–30.
2. Rayner CR, *et al.* Population pharmacokinetics of oseltamivir when coadministered with probenecid. *J Clin Pharmacol* 2008; 48: 935–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agripan; Agucort; Tamiflu; Veltamir; ***Austral.***: Tamiflu; ***Austria***: Tamiflu; ***Belg.***: Tamiflu; ***Braz.***: Tamiflu; ***Canad.***: Tamiflu; ***Chile***: Euvirax; Rimivat; Tamiflu; Virobin; ***China***: Ao Er Fei (奥尔菲); Ke Wei (可威); Ou Rui Si (欧瑞斯); Tamiflu (达菲); *Cz.*: Tamiflu; ***Denm.***: Tamiflu; ***Fin.***: Tamiflu; ***Fr.***: Tamiflu; ***Ger.***: Tamiflu; *Gr.*: Tamiflu; ***Hong Kong***: Tamiflu; ***Hung.***: Tamiflu; ***India***: Fluvir; ***Irl.***: Tamiflu; ***Israel***: Tamiflu; ***Ital.***: Tamiflu; ***Jpn***: Tamiflu; ***Malaysia***: Fluhalt; Omiflu; Tamiflu; ***Mex.***: Tamiflu; ***Neth.***: Tamiflu; ***Norw.***: Tamiflu; ***NZ***: Tamiflu; ***Philipp.***: Tamiflu; ***Pol.***: Tamiflu; ***Port.***: Tamiflu; ***Rus.***: Tamiflu (Тамифлю); ***S.Afr.***: Tamiflu; ***Singapore***: Tamiflu; ***Spain***: Tamiflu; ***Swed.***: Tamiflu; ***Switz.***: Tamiflu; ***Thai.***: GPO-A-Flu; Tamiflu; ***Turk.***: Enfluvir; Tamiflu; ***UAE***: FluFly; ***UK***: Tamiflu; ***Ukr.***: Tamiflu (Тамифлю); ***USA***: Tamiflu.

Pharmacopoeial Preparations
BP 2014: Paediatric Oseltamivir Oral Solution;
USP 36: Oseltamivir Phosphate Capsules.

Penciclovir *(BAN, USAN, rINN)*

BRL-39123; BRL-39123-D (penciclovir sodium); Penciclovirum; Penciklovir; Pensikloviiri; Pensiklovir; Пенцикловир.

9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine.

$C_{10}H_{15}N_5O_3$=253.3

CAS — 39809-25-1 (penciclovir); 97845-62-0 (penciclovir sodium).

ATC — D06BB06; J05AB13.

ATC Vet — QD06BB06; QJ05AB13.

UNII — 359HUE8FJC.

Uses and Administration

Penciclovir is a nucleoside analogue structurally related to guanine, which is active against herpesviruses. It is applied topically as a 1% cream every 2 hours during waking hours for 4 days in the treatment of herpes labialis (see Herpes Simplex Infections, p. 955.2).

For systemic use, penciclovir is given orally as the prodrug famciclovir (see p. 979.1). Intravenous dosage of penciclovir has been investigated.

References.

1. Spruance SL, *et al.* Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. *JAMA* 1997; 277: 1374–9.
2. Lazarus HM, *et al.* Intravenous penciclovir for treatment of herpes simplex infections in immunocompromised patients: results of a multicenter, acyclovir-controlled trial. *Antimicrob Agents Chemother* 1999; 43: 1192–7.
3. Boon R, *et al.* Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2000; 22: 76–90.
4. Raborn GW, *et al.* Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc* 2002; 133: 303–9.
5. Lin L, *et al.* Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. *J Dermatol Treat* 2002; 13: 67–72.

Adverse Effects and Precautions

Penciclovir applied topically may cause transient stinging, burning, and numbness.

For adverse effects of penciclovir after systemic use of famciclovir, see p. 979.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies penciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Antiviral Action

Penciclovir has antiviral activity similar to that of aciclovir (p. 966.1). It is active *in vitro* and *in vivo* against herpes simplex virus types 1 and 2 and against varicella-zoster virus. This activity is due to intracellular conversion by virus-induced thymidine kinase into penciclovir triphosphate, which inhibits replication of viral DNA and persists in infected cells for more than 12 hours. It also has activity against Epstein-Barr virus and hepatitis B virus.

References.

1. Vere-Hodge RA. Famciclovir and penciclovir: the mode of action of famciclovir including its conversion to penciclovir. *Antiviral Chem Chemother* 1993; 4: 67–84.
2. Boyd MR, *et al.* Penciclovir: a review of its spectrum of activity, selectivity, and cross-resistance pattern. *Antiviral Chem Chemother* 1993; 4 (suppl 1): 3–11.
3. Bacon TH, Boyd MR. Activity of penciclovir against Epstein-Barr virus. *Antimicrob Agents Chemother* 1995; 39: 1599–1602.
4. Sarisky RT, *et al.* Profiling penciclovir susceptibility and prevalence of resistance of herpes simplex virus isolates across eleven clinical trials. *Arch Virol* 2003; 148: 1757–69.

Pharmacokinetics

Penciclovir is poorly absorbed from the gastrointestinal tract. For systemic use it is usually given orally as the prodrug famciclovir, which is rapidly converted to penciclovir. Peak plasma concentrations proportional to the dose (over the range 125 to 750 mg) occur after 45 minutes to 1 hour. The plasma elimination half-life is about 2 hours. The intracellular half-life of the active triphosphate metabolite is longer. Penciclovir is less than 20% bound to plasma proteins. Penciclovir is mainly excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pentavir; ***Austral.***: Vectavir; ***Austria***: Famvir; Fenivir; ***Belg.***: Vectavir; *Braz.*: Penvir Labia; Vectavir†; ***Canad.***: Denavir; ***China***: Danpule (丹普乐); Fu Tan (夫坦); Heng Ao Pu Kang (恒奥普康); Keyou (可由); Li Ke Shuang (丽科爽); Li Zhu Jun Le (丽珠君乐); *Cz.*: Vectavir; ***Denm.***: Vectavir; ***Fin.***: Fenistil Pencivir†; ***Gr.***: Fenivir; Vectavir; ***Hung.***: Fenivir; ***Irl.***: Vectavir; ***Israel***: Fenlips; ***Ital.***: Vectavir; Zilip; ***Neth.***: Fenistil Penciclovir; Vectavir†; ***Norw.***: Vectavir; ***Port.***: Denovir†; Fenivir; ***Rus.***: Fenistil Pencivir (Фенистил Пенцивир); ***S.Afr.***: Fenivir†; ***Singapore***: Vectavir; ***Spain***: Fenivir; Vectavir†; ***Swed.***: Vectavir; ***Switz.***: Famvir†; Fenivir; ***Turk.***: Vectavir; ***UK***: Fenistil; Vectavir; ***Ukr.***: Fenistil Pencivir (Фенистил Пенцивир); ***USA***: Denavir.

Peptide T

D-Ala-peptide-T-amide; Péptido T; Пептид Т.

Profile

Peptide T is an octapeptide segment of the envelope glycoprotein of HIV. It has been investigated for the treatment of HIV infection and HIV-associated neurological

disorders. Peptide T has also been tried in the treatment of psoriasis.

Peramivir *(USAN, rINN)*

BCX-1812; Peramivir; Peramivirum; RWJ-270201; Перамивир.

(1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-Acetylamino-2-ethylbutyl]-4-[(aminoiminomethyl)amino]-2-hydroxycyclopentanecarboxylic acid trihydrate.

$C_{15}H_{28}N_4O_4.3H_2O$=382.5

CAS — 229614-55-5 (peramivir monohydrate).

UNII — QW7Y7ZR15U.

Uses and Administration

Peramivir is a neuraminidase inhibitor that is given intravenously; it is being evaluated in phase 3 clinical studies for the treatment of influenza (see p. 960.2). Although it has not yet been approved for marketing, the FDA has authorised the emergency use of peramivir in the USA to treat certain adult and paediatric patients with suspected or laboratory-confirmed pandemic (H1N1) 2009 influenza, or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology.

The recommended dose for patients from 18 years of age is 600 mg given intravenously over 30 minutes once daily for 5 to 10 days. Dose adjustments are needed in patients with renal impairment, see below.

For details of doses in children, see below.

Administration in children. Peramivir may be given to children in the treatment of pandemic (H1N1) 2009 influenza, similarly to adults (see above). Doses may be given intravenously over 60 minutes once daily for 5 to 10 days according to age as follows:

- birth to 30 days old: 6 mg/kg
- 31 to 90 days old: 8 mg/kg
- 91 to 180 days old: 10 mg/kg
- 181 days old to 5 years of age: 12 mg/kg
- 6 to 17 years of age: 10 mg/kg

The maximum daily dose is 600 mg. For details of dose adjustments in children with renal impairment, see below.

Administration in renal impairment. Intravenous doses of peramivir should be reduced in patients with renal impairment, according to creatinine clearance (CC):

Adults from 18 years of age.

- CC 31 to 49 mL/minute: 150 mg daily
- CC 10 to 30 mL/minute: 100 mg daily
- CC less than 10 mL/minute: 100 mg on day 1, then 15 mg daily thereafter
- Intermittent haemodialysis: 100 mg on day 1, and 2 hours after the end of each dialysis session

Infants and children.

- CC 31 to 49 mL/minute per 1.73 m^2:
  - 1.5 mg/kg daily in those from birth to 30 days old
  - 2 mg/kg daily in those from 31 to 90 days old
  - 2.5 mg/kg daily in those from 91 to 180 days old
  - 3 mg/kg daily in those from 181 days old to 5 years of age
  - 2.5 mg/kg daily in those from 6 to 17 years of age
- CC 10 to 30 mL/minute per 1.73 m^2:
  - 1 mg/kg daily in those from birth to 30 days old
  - 1.3 mg/kg daily in those from 31 to 90 days old
  - 1.6 mg/kg daily in those from 91 to 180 days old
  - 1.9 mg/kg daily in those from 181 days old to 5 years of age
  - 1.6 mg/kg daily in those from 6 to 17 years of age
- CC less than 10 mL/minute per 1.73 m^2:
  - 1 mg/kg on day 1, then 0.15 mg/kg daily in those from birth to 30 days old
  - 1.3 mg/kg on day 1, then 0.2 mg/kg daily in those from 31 to 90 days old
  - 1.6 mg/kg on day 1, then 0.25 mg/kg daily in those from 91 to 180 days old
  - 1.9 mg/kg on day 1, then 0.3 mg/kg daily in those from 181 days to 5 years of age
  - 1.6 mg/kg on day 1, then 0.25 mg/kg daily in those from 6 to 17 years of age
- For children on intermittent haemodialysis, the following doses, based on age and weight, are given on day 1, and then 2 hours after each dialysis session:
  - 1 mg/kg for those from birth to 30 days old
  - 1.3 mg/kg for those from 31 to 90 days old
  - 1.6 mg/kg for those from 91 to 180 days old
  - 1.9 mg/kg for those from 181 days to 5 years of age
  - 1.6 mg/kg for those from 6 to 17 years of age

Adverse Effects

Safety and efficacy data for peramivir are limited. The most commonly reported adverse events have been diarrhoea, nausea, vomiting, and neutropenia. Although not seen in clinical studies to date the FDA considers that it may rarely cause anaphylaxis or serious skin reactions. As with other neuraminidase inhibitors, neurologic and behavioral symptoms have been infrequently reported. For further information on neurological and other adverse effects associated with neuraminidase inhibitors, see under Oseltamivir, p. 1007.2.

Patients with known or suspected renal insufficiency should have a baseline creatinine clearance measurement before taking peramivir. Dosage adjustments may be necessary in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Rapiacta.

Pleconaril *(USAN, rINN)*

Pléconaril; Pleconarilo; Pleconarilum; VP-63843; Win-63843; Плеконарил.

3-[4-[3-(3-Methyl-5-isoxazolyl)propoxy]-3,5-xylyl]-5-(trifluoromethyl)-1,2,4-oxadizole.

$C_{18}H_{18}F_3N_3O_3$=381.4

CAS — 153168-05-9.

ATC — J05AX06.

ATC Vet — QJ05AX06.

UNII — 9H4570Q89D.

Profile

Pleconaril is an antiviral with activity against a range of picornaviruses. It has been investigated for the oral treatment of viral meningitis and encephalitis, upper respiratory-tract viral infections, and other enteroviral infections. However, there have been concerns over efficacy, viral resistance, and interactions with oral contraceptives. Development of an intranasal formulation for the common cold has also been investigated.

References.

1. Nowak-Wegrzyn A, *et al.* Successful treatment of enterovirus infection with the use of pleconaril in 2 infants with severe combined immunodeficiency. *Clin Infect Dis* 2001; 32: E13–E14.
2. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001; 32: 228–35.
3. Aradottir E, *et al.* Severe neonatal enteroviral hepatitis treated with pleconaril. *Pediatr Infect Dis J* 2001; 20: 457–9.
4. Starlin R, *et al.* Acute flaccid paralysis syndrome associated with echovirus 19, managed with pleconaril and intravenous immunoglobulin. *Clin Infect Dis* 2001; 33: 730–2.
5. Hayden FG, *et al.* Oral pleconaril treatment of picornavirus-associated viral respiratory illness in adults: efficacy and tolerability in phase II clinical trials. *Antivir Ther* 2002; 7: 53–65.
6. Abzug MJ, *et al.* Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Pediatr Infect Dis J* 2003; 22: 335–41.
7. Hayden FG, *et al.* Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. *Clin Infect Dis* 2003; 36: 1523–32.
8. Webster AD. Pleconaril—an advance in the treatment of enteroviral infection in immuno-compromised patients. *J Clin Virol* 2005; 32: 1–6.
9. Desmond RA, *et al.* Enteroviral meningitis: natural history and outcome of pleconaril therapy. *Antimicrob Agents Chemother* 2006; 50: 2409–14.

Poly I.poly C12U

Poli(I)·poli(C_{12}U); Poly(I):poly(C_{12}U); Поли I.Поли C12U.

Profile

Poly I.poly C12U is a synthetic mismatched polymer of double-stranded RNA with antiviral and immunomodulatory activity (see also Poly I. Poly C, p. 2594.1). It is under investigation in the treatment of HIV infection, and also in renal cell carcinoma, chronic fatigue syndrome, invasive melanoma, and hepatitis B and C.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ampligen.

Propagermanium *(rINN)*

Propagermanio; Пропагерманий.

A polymer obtained from 3-(trihydroxygermyl)propionic acid.

$(C_3H_5GeO_{3.5})_n$

CAS — 12758-40-6.

Profile

Propagermanium is an immunomodulator that has been used in chronic hepatitis B infections. Acute exacerbation of hepatitis, including some fatalities, has been reported in patients receiving propagermanium.

References.

1. Hirayama C, *et al.* Propagermanium: a nonspecific immune modulator for chronic hepatitis B. *J Gastroenterol* 2003; 38: 525–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Serocion.

Raltegravir *(BAN, USAN, rINN)*

Raltégravir; Raltegravirum; Raltegrawir; Ральтегравир.

N-[2-[4-(4-Fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]-5-methyl-1,3,4-oxadiazole-2-carboxamide.

$C_{20}H_{21}FN_6O_5$=444.4

CAS — 518048-05-0.

ATC — J05AX08.

ATC Vet — QJ05AX08.

UNII — 22VKVB053U.

Raltegravir Potassium *(BANM, USAN, rINNM)*

Kalii Raltegravirum; MK-0518; Raltegravir potásico; Raltégravir Potassique; Калия Ральтегравир.

Potassium 4-[(4-fluorobenzyl)carbamoyl]-1-methyl-2-(1-methyl-1-[[5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino)ethyl)-6-oxo-1,6-dihydropyrimidin-5-olate.

$C_{20}H_{20}FKN_6O_5$=482.5

CAS — 871038-72-1.

UNII — 43Y000U234.

Uses and Administration

Raltegravir is an inhibitor of HIV integrase, an enzyme essential for insertion of viral DNA into the host genome, and thus for replication. It is used with other antiretrovirals for treatment of HIV infection and AIDS (p. 957.2) and is licensed for use in both treatment-naive and treatment-experienced patients.

It is given orally as the potassium salt but doses are expressed in terms of the base; 434 mg of raltegravir potassium is equivalent to about 400 mg of raltegravir. The usual dose is the equivalent of 400 mg of raltegravir twice daily, with or without food. For details of doses in children and adolescents, see below.

Doses of raltegravir may need to be amended when given with rifampicin: a dose of 800 mg twice daily has been suggested.

References.

1. Iwamoto M, *et al.* Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. *Clin Pharmacol Ther* 2008; 83: 293–9.
2. Croxtall JD, *et al.* Raltegravir. *Drugs* 2008; 68: 131–8.
3. Croxtall JD, Keam SJ. Raltegravir: a review of its use in the management of HIV infection in treatment-experienced patients. *Drugs* 2009; 69: 1059–75.
4. Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clin Infect Dis* 2009; 48: 931–9.
5. Lennox JL, *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; 374: 796–806. Correction. *ibid.*: 786.
6. Croxtall JD, Scott LJ. Raltegravir: in treatment-naive patients with HIV-1 infection. *Drugs* 2010; 70: 631–42.
7. Steigbigel RT, *et al.* BENCHMRK Study Teams. Long-term efficacy and safety of raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 phase III trials. *Clin Infect Dis* 2010; 50: 605–12.
8. Ramkumar K, Neamati N. Raltegravir: the evidence of its therapeutic value in HIV-1 infection. *Core Evid* 2010; 4: 131–47.
9. Skiest DJ, *et al.* Similar efficacy of raltegravir when used with or without a protease inhibitor in treatment-experienced patients. *HIV Clin Trials* 2011; 12: 131–40.
10. Brainard DM, *et al.* Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J Clin Pharmacol* 2011; 51: 1376–1402.
11. Rokas KEE, *et al.* Role of raltegravir in HIV-1 management. *Ann Pharmacother* 2012; 46: 578–89.

Administration in children. For the treatment of HIV infection in children from 2 years of age and adolescents raltegravir is given with other antiretroviral drugs. In the USA, oral *film-coated* or *chewable* tablets are available; the two formulations are not interchangeable as the chewable tablet has a higher bioavailability compared with the film-coated tablets. Doses are based on body-weight.

In children from 2 years (and weighing at least 10 kg) to less than 12 years of age, the following dose recommendations are made for *chewable tablets*:

- 10 to less than 14 kg: 75 mg twice daily
- 14 to less than 20 kg: 100 mg twice daily
- 20 to less than 28 kg: 150 mg twice daily
- 28 to less than 40 kg: 200 mg twice daily
- at least 40 kg: 300 mg twice daily (maximum dose)

Film-coated tablets may be given to children from 6 years of age (and weighing at least 25 kg) and adolescents; the usual oral dose is 400 mg twice daily.

Adverse Effects and Precautions

On the basis of limited data, raltegravir appears to be well tolerated; non-specific adverse effects associated with raltegravir-based regimens include rash, insomnia, abnormal dreams, headache, abdominal pain, diarrhoea, nausea, vomiting, asthenia, fatigue, dizziness, and vertigo. Rarely, more serious adverse effects such as immune reconstitution syndrome, gastritis, hepatitis, renal failure, neutropenia, thrombocytopenia, and hypersensitivity and severe skin reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis have occurred. Psychiatric disturbances, including anxiety, depression, paranoia, and suicidal ideation have also been reported, particularly in those with a pre-existing history of mental illness. Abnormal creatine phosphokinase values may occur and myopathy and rhabdomyolysis have been reported although a causal relationship has not been established; nonetheless, caution is advised in patients at increased risk of these conditions. Increased liver transaminases and serum triglyceride concentrations may also occur.

Interactions

Raltegravir is not a substrate for cytochrome P450 isoenzymes, and does not appear to interact with drugs metabolised by this mechanism. However, rifampicin induces the glucuronidase responsible for raltegravir metabolism (UGT1A1) and reduces plasma concentrations of raltegravir; if use with rifampicin cannot be avoided, increasing the dose of raltegravir may be considered (see Uses and Administration, p. 1009.3).

Antivirals. Plasma concentrations of raltegravir were modestly increased by *atazanavir* and ritonavir-boosted atazanavir in healthy subjects; this increase is not considered to be clinically significant.[1]

In a pharmacokinetic study, use of raltegravir and *maraviroc* together resulted in decreased plasma concentrations of both drugs, although these changes were also not thought to be clinically significant.[2]

1. Iwamoto M, *et al.* Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *Clin Infect Dis* 2008; 47: 137–40.
2. Andrews E, *et al.* Assessment of the pharmacokinetics of co-administered maraviroc and raltegravir. *Br J Clin Pharmacol* 2010; 69: 51–7.

Gastrointestinal drugs. The solubility of raltegravir is pH-dependent, and use of *omeprazole* has been noted to increase plasma concentrations of raltegravir in healthy subjects.[1] However, some HIV-infected patients (and particularly those with AIDS) have increased gastric pH relating to their illness, and data from HIV-infected patients suggests acceptable safety and only modest pharmacokinetic interaction when gastric-acid reducing drugs are used with raltegravir.[1] US licensed product information for raltegravir therefore suggests that no dose adjustment is needed when raltegravir is used with gastric-acid reducing drugs, although UK licensed information has advised that such combinations should be avoided unless considered essential.

1. Iwamoto M, *et al.* Effects of omeprazole on plasma levels of raltegravir. *Clin Infect Dis* 2009; 48: 489–92.

Pharmacokinetics

Raltegravir is absorbed on oral dosage and peak concentrations occur after 3 hours. There is considerable interindividual variation in the pharmacokinetics. It is metabolised via glucuronidation, catalysed by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and excreted in both urine and faeces as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Isentress; ***Austria***: Isentress; ***Belg.***: Isentress; ***Braz.***: Isentress; ***Canad.***: Isentress; ***Chile***: Isentress; ***China***: Isentress (艾生特); Cz.: Isentress; ***Denm.***: Isentress; ***Fr.***: Isentress; ***Ger.***: Isentress; ***Gr.***: Isentress; ***Hong Kong***: Isentress; ***Hung.***: Isentress; ***Irl.***: Isentress; ***Israel***: Isentress; ***Ital.***: Isentress; ***Malaysia***: Isentress; ***Neth.***: Isentress; ***Norw.***: Isentress; ***NZ***: Isentress; ***Pol.***: Isentress; ***Port.***: Isentress; ***Rus.***: Isentress (Исентресс); ***Singapore***: Isentress; ***Spain***: Isentress; ***Swed.***: Isentress; ***Switz.***: Isentress; ***Thai.***: Isentress; ***UK***: Isentress; ***Ukr.***: Isentress (Исентресс); ***USA***: Isentress.

Resiquimod *(rINN)*

R-848; Resiquimod; Resiquimodum; S-28463; VML-600; Резиквимод.

4-Amino-2-(ethoxymethyl)-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

$C_{17}H_{22}N_4O_2$=314.4

CAS — 144875-48-9.

UNII — V3DMU7PVXF.

Profile

Resiquimod is an immune response modifier that has been investigated for the topical treatment of genital herpes, common warts, and actinic keratosis. It is also being studied as a potential adjunct therapy for improving the immune response to certain vaccines.

References.

1. Spruance SL, *et al.* Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. *J Infect Dis* 2001; 184: 196–200.
2. Mark KE, *et al.* Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: a randomized, controlled trial. *J Infect Dis* 2007; 195: 1324–31.
3. Szeimies RM, *et al.* A phase II dose-ranging study of topical resiquimod to treat actinic keratosis. *Br J Dermatol* 2008; 159: 205–10.
4. Igartua M, Pedraz JL. Topical resiquimod: a promising adjuvant for vaccine development? *Expert Rev Vaccines* 2010; 9: 23–7.

Ribavirin *(BAN, USAN, rINN)*

ICN-1229; Ribaviriini; Ribavirina; Ribavirinas; Ribavirine; Ribavirinum; RTCA; Tribavirin; Рибавирин.

1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

$C_8H_{12}N_4O_5$=244.2

CAS — 36791-04-5.

ATC — J05AB04.

ATC Vet — QJ05AB04.

UNII — 49717AWG6K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Ribavirin). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; slightly soluble or very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.5. Protect from light.

USP 36: (Ribavirin). A white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. Store in airtight containers.

Uses and Administration

Ribavirin is a synthetic nucleoside analogue structurally related to guanine. It is given by aerosol in the treatment of RSV infections (p. 961.3); this route appears to give better results than the oral route although its efficacy is questionable. It is used orally with an interferon alfa or peginterferon alfa in the treatment of chronic hepatitis C (p. 990.3), including HIV co-infection. Ribavirin has been tried in haemorrhagic fevers, such as haemorrhagic fever with renal syndrome and Lassa fever (p. 1011.1), and in SARS (p. 962.2).

For details of doses in children, see below.

Ribavirin is used, with an interferon alfa or peginterferon alfa, for the treatment of chronic **hepatitis C**. For information on the dose of interferon alfa used in the treatment of chronic hepatitis C see under Interferon Alfa, p. 989.2. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In those with hepatitis C infection alone (*mono-infection*), patients with viral genotype 1, and probably genotype 4, should generally be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks; data on genotypes 5 or 6 are insufficient to make recommendations. In *co-infection* with HIV, treatment should generally be given for 48 weeks regardless of genotype.

Rebetol (Schering-Plough) is used, with interferon alfa-2b or peginterferon alfa-2b for hepatitis C.

The following doses are recommended in the UK:

- adults up to 65 kg: 400 mg both in the morning and in the evening
- 65 to 80 kg: 400 mg in the morning and 600 mg in the evening
- from 81 to 105 kg: 600 mg both in the morning and in the evening
- over 105 kg: 600 mg in the morning and 800 mg in the evening

In the USA, the dose of ribavirin given with interferon alfa-2b is:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

The following doses are used with peginterferon alfa-2b:

- adults up to 65 kg: 400 mg both in the morning and in the evening
- from 66 to 80 kg: 400 mg in the morning and 600 mg in the evening
- from 81 to 105 kg: 600 mg both in the morning and in the evening
- from 105 kg: 600 mg in the morning and 800 mg in the evening

Copegus (Roche) is used in the UK with interferon alfa-2a or peginterferon alfa-2a and in the USA with peginterferon alfa-2a.

The following doses are used with peginterferon alfa-2a for mono-infection in genotype 1 or 4:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For mono-infection in genotype 2 or 3 (with peginterferon alfa-2a):

- all adults: 400 mg both in the morning and in the evening

The following doses are used with interferon alfa-2a for mono-infection in genotype 1 or 4:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For co-infection with HIV:

- all adults: 800 mg daily, irrespective of genotype

Dose reductions of ribavirin may be necessary in patients who develop low haemoglobin concentrations. Ribavirin is contra-indicated in patients with a creatinine clearance less than 50 mL/minute.

Reviews.

1. Gish RG. Treating HCV with ribavirin analogues and ribavirin-like molecules. *J Antimicrob Chemother* 2006; 57: 8–13.
2. Gambarin-Gelwan M, Jacobson IM. Optimal dose of peginterferon and ribavirin for treatment of chronic hepatitis C. *J Viral Hepatitis* 2008; 15: 623–33.
3. Reddy KR, *et al.* Ribavirin: current role in the optimal clinical management of chronic hepatitis C. *J Hepatol* 2009; 50: 402–11.
4. Shiffman ML. What future for ribavirin? *Liver Int* 2009; 29 (suppl 1): 68–73.
5. Brok J, *et al.* Ribavirin monotherapy for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 22/01/10).
6. Aghemo A, *et al.* Pegylated IFN-α 2a and ribavirin in the treatment of hepatitis C. *Expert Rev Anti Infect Ther* 2009; 7: 925–35.
7. Gluud LL, *et al.* Peginterferon plus ribavirin for chronic hepatitis C in patients with human immunodeficiency virus. *Am J Gastroenterol* 2009; 104: 2335–41.
8. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children (withdrawn). Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 18/08/10).

Administration. Reference[1] to the intravenous use of ribavirin.

1. Riner A, *et al.* Intravenous ribavirin—review of the FDA's Emergency Investigational New Drug Database (1997-2008) and literature review. *Postgrad Med* 2009; 121: 139–46.

Administration in children. Preparations of ribavirin are available for aerosol administration to infants and children with severe **RSV** infection via a small particle aerosol generator. Solutions containing 20 mg/mL are used; 300 mL, representing 6 g of ribavirin, is delivered over a 12-to 18-hour period by aerosol at an average concentration of 190 micrograms/litre of air. Treatment is given for 3 to 7 days.

Ribavirin is used, with an interferon alfa or peginterferon alfa, for the treatment of chronic **hepatitis C**. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In hepatitis C mono-infection, patients with viral genotype 1 should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks.

Rebetol (Schering-Plough) is used, with interferon alfa-2b or peginterferon alfa-2b, for hepatitis C.

The following doses are recommended in the UK for children 3 years of age and older:

- less than 47 kg: 15 mg/kg daily in 2 divided doses
- 47 to 49 kg: 200 mg in the morning and 400 mg in the evening
- 50 to 65 kg: 400 mg both in the morning and in the evening
- over 65 kg: the adult dose (above)

In the USA, ribavirin is licensed for use with interferon alfa-2b and peginterferon alfa-2b, for the treatment of children from 3 to 17 years of age. The recommended doses of ribavirin are:

- less than 47 kg: 15 mg/kg daily
- 47 to 59 kg: 400 mg both in the morning and in the evening
- 60 to 73 kg: 400 mg in the morning and 600 mg in the evening
- over 73 kg: 600 mg both in the morning and in the evening

Copegus (Roche) is not licensed for use in those less than 18 years of age.

For information on the dose of interferon alfa used in the treatment of chronic hepatitis C in children see under Interferon Alfa, p. 990.1.

Encephalitis. A beneficial response to ribavirin was reported in a child with severe La Crosse encephalitis.

Ribavirin was given intravenously in a dose of 25 mg/kg over the first 24 hours and then reduced to 15 mg/kg daily for a further 9 days. A small open-label study[2] suggested that ribavirin might also be able to reduce mortality and neurological deficits in acute Nipah encephalitis. However, oral ribavirin was not effective in reducing mortality in children with Japanese encephalitis.[3]

Intraventricular ribavirin (plus intraventricular interferon and oral isoprinosine) was found to be effective in 4 of 5 patients with subacute sclerosing panencephalitis.[4] A concentration of ribavirin in the CSF of 50 to 200 micrograms/mL completely inhibited viral replication; doses of ribavirin given to achieve this concentration ranged from 1 to 9 mg/kg daily.

1. McJunkin JE, *et al.* Treatment of severe La Crosse encephalitis with intravenous ribavirin following diagnosis by brain biopsy. *Pediatrics* 1997; **99:** 261–7.
2. Chong HT, *et al.* Treatment of acute Nipah encephalitis with ribavirin. *Ann Neurol* 2001; **49:** 810–13.
3. Kumar R, *et al.* Randomized, controlled trial of oral ribavirin for Japanese encephalitis in children in Uttar Pradesh, India. *Clin Infect Dis* 2009; **48:** 400–6.
4. Hosoya M, *et al.* Pharmacokinetics and effects of ribavirin following intraventricular administration for treatment of subacute sclerosing panencephalitis. *Antimicrob Agents Chemother* 2004; **48:** 4631–5.

Haemorrhagic fevers. The treatment of haemorrhagic fevers (p. 952.1) is mainly symptomatic. However, ribavirin has been reported to reduce mortality in patients with Lassa fever,[1] haemorrhagic fever with renal syndrome,[2] and possibly Crimean-Congo haemorrhagic fever[3-5] and Bolivian haemorrhagic fever.[6] Intravenous ribavirin has also been tried in the related hantavirus pulmonary syndrome,[7,8] but a small randomised, double-blind, placebo-controlled study[9] with intravenous ribavirin reported no significant difference in survival between the 2 groups.

For treatment of *Lassa fever*, ribavirin has been given intravenously in a dose of 2 g initially, then 1 g every 6 hours for 4 days, then 500 mg every 8 hours for 6 days.[1] Treatment is most effective if started within 6 days of the onset of fever. Experience has shown that rigors may occur if the drug is given as a bolus injection, but that this can be overcome by giving it as an infusion over 30 minutes.[10] For prophylaxis, an oral dose of ribavirin 600 mg 4 times daily for 10 days has been suggested for adults,[11] although this was considered to be excessive by other commentators[12] who suggested that oral doses of 1 g daily (after an intravenous loading dose for those in whom the start of prophylaxis is delayed) might be suitable.

1. McCormick JB, *et al.* Lassa fever: effective therapy with ribavirin. *N Engl J Med* 1986; **314:** 20–6.
2. Huggins JW, *et al.* Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis* 1991; **164:** 1119–27.
3. Fisher-Hoch SP, *et al.* Crimean Congo-haemorrhagic fever treated with oral ribavirin. *Lancet* 1995; **346:** 472–5.
4. Mardani M, *et al.* The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. *Clin Infect Dis* 2003; **36:** 1613–18.
5. Soares-Weiser K, *et al.* Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis. *BMC Infect Dis* 2010; **10:** 207.
6. Kilgore PE, *et al.* Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 1997; **24:** 718–22.
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8. Prochoda K, *et al.* Hantavirus-associated acute respiratory failure. *N Engl J Med* 1993; **329:** 1744.
9. Mertz GJ, *et al.* Collaborative Antiviral Study Group. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis* 2004; **39:** 1307–13.
10. Fisher-Hoch SP, *et al.* Unexpected adverse reactions during a clinical trial in rural West Africa. *Antiviral Res* 1992; **19:** 139–47.
11. Holmes GP, *et al.* Lassa fever in the United States: investigation of a case and new guidelines for management. *N Engl J Med* 1990; **323:** 1120–23.
12. Johnson KM, Monath TP. Imported Lassa fever—reexamining the algorithms. *N Engl J Med* 1990; **323:** 1139–41.

Adverse Effects

When given *by inhalation*, ribavirin has sometimes led to worsening of lung function, bacterial pneumonia, and pneumothorax, to cardiovascular effects (including a fall in blood pressure and cardiac arrest), and, rarely, to anaemia, haemolysis, and reticulocytosis. Conjunctivitis and skin rash have also occurred. Precipitation of inhaled ribavirin and consequent accumulation of fluid has occurred in the tubing of ventilating equipment.

The most common adverse effects reported by patients taking *oral* ribavirin, with either interferon alfa or peginterferon alfa, are psychiatric reactions (such as anxiety, depression, insomnia, and irritability) and flu-like symptoms. Life-threatening or fatal adverse effects include severe depression, suicidal ideation, relapse of drug abuse or overdose, and bacterial infection. Severe adverse effects include haemolytic anaemia, leucopenia, thrombocytopenia, aplastic anaemia, diabetes mellitus, auto-immune disorders, gastrointestinal symptoms, pancreatitis, pulmonary embolism, chest pain, liver dysfunction, and interstitial pneumonitis. Lupus erythematosus, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), and photosensitivity have also been reported. Growth retardation (including decrease in height and weight) has been reported in children. Many varied adverse effects may occur as a result of the use of ribavirin with interferon alfa (see under Adverse Effects in Interferon Alfa, p. 992.2).

Incidence of adverse effects. A review[1] of adverse effects reported in 110 patients with suspected or probable SARS who were treated with ribavirin found that 61% of the patients had evidence of haemolytic anaemia. In a smaller cohort of 76 patients hypocalcaemia and hypomagnesaemia were reported in 58% and 46% of patients, respectively, while 29% had evidence of both hypocalcaemia and hypomagnesaemia. A retrospective cohort study[2] found that the adverse effects strongly associated with the use of ribavirin (mostly high-dose) in 306 patients with confirmed or probable SARS, were progressive anaemia, hypomagnesaemia, and bradycardia.

1. Knowles SR, *et al.* Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis* 2003; **37:** 1139–42.
2. Muller MP, *et al.* Canadian SARS Research Network. Adverse events associated with high-dose ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome. *Pharmacotherapy* 2007; **27:** 494–503.

Precautions

SPECIFIC CAUTIONS FOR INHALED TREATMENT. Standard supportive respiratory and fluid management should be maintained during aerosol treatment with ribavirin and electrolytes should be monitored closely. Equipment should be monitored for precipitation of ribavirin. Precautions should be taken to minimise atmospheric pollution with ribavirin during aerosol inhalation.

SPECIFIC CAUTIONS FOR ORAL TREATMENT. Ribavirin should not be given orally to patients with pre-existing medical conditions that could be exacerbated by ribavirin-induced haemolysis, including significant or unstable cardiac disease or haemoglobinopathies (thalassaemia or sickle-cell anaemia). Blood cell counts and chemistry should be measured at the start of treatment, after 2 and 4 weeks of treatment, and periodically thereafter. Patients with renal impairment and a creatinine clearance of less than 50 mL/minute should not receive oral ribavirin. It should be avoided in patients with severe hepatic impairment or decompensated cirrhosis of the liver (Child-Pugh 6 or more). The potential for development of gout should be considered in predisposed patients. Patients should be monitored for signs and symptoms of psychiatric disorders. Ribavirin therapy is contra-indicated in children and adolescents with a history of, or existing, psychiatric disorders. The growth of children should be monitored and thyroid function should be tested every 3 months. Patients infected with hepatitis C virus and HIV should be carefully monitored for signs of mitochondrial toxicity and lactic acidosis. Dental and periodontal disorders have been reported and regular dental examinations and good oral hygiene are advised.

Contact lenses. Report of damage to a nurse's soft contact lenses after intermittent occupational exposure to aerosolised ribavirin over a period of 1 month.[1]

1. Diamond SA, Dupuis LL. Contact lens damage due to ribavirin exposure. *DICP Ann Pharmacother* 1989; **23:** 428–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ribavirin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Oral ribavirin has been reported to be teratogenic and embryocidal in *rodents* and is contra-indicated in pregnancy or in those who may become pregnant. Ribavirin was not found to be teratogenic in *baboons*. Although there are no case reports of teratogenicity after exposure to aerosolised ribavirin during pregnancy, licensed product information advises that pregnant women and those planning pregnancy should avoid exposure to the aerosol. Pregnancy should also be avoided in partners of male patients taking ribavirin orally. Effective contraception should be used during treatment and for 6 months after the end of treatment. Male patients whose partners are pregnant should use a condom to minimise vaginal exposure to ribavirin.

Interactions

Use of ribavirin with zidovudine is not recommended as patients are at increased risk of anaemia. Increased toxicity has also been seen with didanosine, and the combination should be avoided. Ribavirin inhibits the phosphorylation of NRTIs such as zidovudine, lamivudine, and stavudine, but although UK licensed product information suggests this may reduce their activity against HIV, US product information indicates that no such reduction has been seen in practice.

Anticoagulants. For reference to the effect of ribavirin on the activity of *warfarin*, see under Antivirals, p. 1533.1.

Antiviral Action

Ribavirin inhibits many viruses *in vitro* and in *animal* models. However, this activity has not necessarily correlated with activity against human infections. Ribavirin is phosphorylated but its mode of action is still unclear; it may act at several sites, including cellular enzymes, to interfere with viral nucleic acid synthesis. The mono- and triphosphate derivatives are believed to be responsible for its antiviral activity. Susceptible DNA viruses include herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae group, influenza, parainfluenza, measles, mumps, and RSV, and HIV.

Pharmacokinetics

Aerosolised ribavirin is absorbed systemically, but local concentrations in the respiratory tract secretions are much higher than plasma concentrations. Plasma half-life is about 9.5 hours. The bioavailability of aerosolised ribavirin is unknown and may depend on the mode of delivery.

Ribavirin is rapidly absorbed after oral doses and peak plasma concentrations occur within 1 to 2 hours. Absorption is extensive but oral bioavailability is about 45 to 65% as a result of first-pass metabolism. Steady state plasma concentrations occur after about 4 weeks with twice-daily oral doses resulting in peak plasma concentrations 6 times higher than that after single doses. On stopping dosing the plasma half-life is about 300 hours as a result of slow elimination from non-plasma compartments. Ribavirin does not bind to plasma proteins. Ribavirin is not metabolised by the cytochrome P450 system; it is metabolised by reversible phosphorylation and degradation involving deribosylation and amide hydrolysis to give a triazole carboxyacid metabolite. After a single oral dose the terminal half-life is about 120 to 170 hours. Ribavirin is mainly excreted in the urine as unchanged drug and metabolites. Insignificant amounts of the drug are removed by haemodialysis.

References.

1. Kramer TR, *et al.* Hemodialysis clearance of intravenously administered ribavirin. *Antimicrob Agents Chemother* 1990; **34:** 489–90.
2. Glue P, *et al.* The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. *Br J Clin Pharmacol* 2000; **49:** 417–21.
3. Tsubota A, *et al.* Pharmacokinetics of ribavirin in combined interferon-alpha 2b and ribavirin therapy for chronic hepatitis C virus infection. *Br J Clin Pharmacol* 2003; **55:** 360–7.
4. Kamar N, *et al.* Ribavirin pharmacokinetics in renal and liver transplant patients: evidence that it depends on renal function. *Am J Kidney Dis* 2004; **43:** 140–6.
5. Uchida M, *et al.* Assessment of adverse reactions and pharmacokinetics of ribavirin in combination with interferon alpha-2b in patients with chronic hepatitis C. *Drug Metab Pharmacokinet* 2004; **19:** 438–43.
6. Wade JR, *et al.* Pharmacokinetics of ribavirin in patients with hepatitis C virus. *Br J Clin Pharmacol* 2006; **62:** 710–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Copegus; Laztie†; Ribavirol; Vibuzol; Xilopar; *Austral.*: Rebetol; Virazide†; *Austria*: Copegus; Rebetol; *Belg.*: Copegus; Rebetol; Virazole; *Braz.*: Ribav; Viramid; Virazole; *Canad.*: Virazole; *Chile*: Rebetol; *China*: Altissum (奥得清); Ao Jia (奥佳); Bang Qing (邦庆); Da Chang (达畅); Hua Le Sha (华乐沙); Jun Da Tan (均达坦); Li Li De (利力德); Li Li Ning (利力宁); Li Mai Xin (利迈欣); Nai De (奈德); Nanyuan (南元); Qi Li Qing (奇力青); Rui Di (锐迪); Tong Xin (同欣); Wei La Ke (维拉克); Wei Li Ning (威利宁); Wei Lin (威林); Wei Rui Ke (威锐克); Weilexing (威乐星); Xinweiling (信韦灵); *Cz.*: Copegus; Rebetol; *Denm.*: Copegus; Rebetol; *Fin.*: Copegus; Rebetol; *Fr.*: Copegus; Rebetol; *Ger.*: Copegus; Rebetol; Virazole; *Gr.*: Copegus; Rebetol; Virazole; *Hong Kong*: Copegus; Rebetol; Virazole; *Hung.*: Copegus; Rebetol; *India*: Ribavin; *Indon.*: Hepaviral; Rebetol; Virazide; *Irl.*: Copegus; Rebetol; *Israel*: Copegus; Rebetol; *Ital.*: Copegus; Rebetol; Virazole; *Jpn*: Copegus; Rebetol; *Malaysia*: Copegus; Rebetol; *Mex.*: Copegus; Desiken; Trivorin; Varinar; Vilona; Virazide; *Neth.*: Copegus; Rebetol; Vilarib; Virazole; *Norw.*: Copegus; Rebetol; *NZ*: Copegus; Rebetol; *Philipp.*: Rebetol; Ribazole; *Pol.*: Copegus; Rebetol; *Port.*: Copegus; Rebetol; *Rus.*: Arviron (Арвирон)†; Rebetol (Ребетол); Ribamidil (Рибамидил); Ribapeg (Рибапег); Ribavin (Рибавин); Trivorin (Триворин); Virazole (Виразол); *S.Afr.*: Copegus; *Singapore*: Copegus; Rebetol; Virazole; *Spain*: Copegus; Rebetol; Virazole; *Swed.*: Copegus; Rebetol; Virazole; *Switz.*: Copegus; Rebetol; *Thai.*: Copegus; Rebetol; *Turk.*: Copegus; Rebetol; Ribasphere; Viron; *UK*: Copegus; Rebetol; Virazole; *Ukr.*: Copegus (Копегус); Livel (Ливел); Rebetol (Ребетол); *USA*: Copegus; Rebetol; RibaPak†; Ribasphere; Ribaspheres; Ribatab†; Virazole; *Venez.*: Rebetol.

Multi-ingredient Preparations. *Arg.*: Bioferon Hepakit; *Austral.*: Pegasys RBV; Pegatron; Rebetron†; *Canad.*: Pegasys RBV; Pegetron; *Hong Kong*: Rebetron†; *Mex.*: Hepatron C†; Pegtron

Cotronak Kit; *NZ*: Pegasys RBV; Pegatron; Rebetron†; Roferon-A RBV; *Philipp.*: Pegasys RBV.

Pharmacopoeial Preparations
BP 2014: Ribavirin Powder for Nebuliser Solution;
USP 36: Ribavirin Capsules; Ribavirin for Inhalation Solution; Ribavirin Tablets.

Rilpivirine *(USAN, rINN)*

R-278474; Rilpivirin; Rilpivirina; Rilpivirinum; TMC-278; Рильпивирин.
4-[(4-[(1E)-2-Cyanoethenyl]-2,6-dimethylphenyl)amino]pyrimidin-2-yl)amino)benzonitrile.
$C_{22}H_{18}N_6$=366.4
CAS — 500287-72-9.
ATC — J05AG05.
ATC Vet — QJ05AG05.
UNII — FI96A8X663.

Rilpivirine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de rilpivirina; Rilpivirine, Chlorhydrate de; Rilpivirini Hydrochloridum; Рильпивирина Гидрохлорид.
$C_{22}H_{18}N_6$,HCl=402.9
CAS — 700361-47-3.
ATC — J05AG05.
ATC Vet — QJ05AG05.
UNII — 212WAX8KDD.

Uses and Administration

Rilpivirine is a second-generation, diarylpyrimidine NNRTI with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when rilpivirine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

Rilpivirine is given orally as the hydrochloride, but doses are expressed in terms of rilpivirine; 27.5 mg of rilpivirine hydrochloride is equivalent to about 25 mg of rilpivirine. It is given with food in a dose of 25 mg daily with a once-daily NRTI regimen.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. A co-formulated tablet containing rilpivirine, emtricitabine, and tenofovir (sometimes referred to as 'Btripla') is available in some countries. A slow-release, parenteral formulation is also under investigation for extended-interval intramuscular or subcutaneous use.

References.

1. Pozniak AL, *et al.* Efficacy and safety of TMC278 in antiretroviral-naive HIV-1 patients: week 96 results of a phase IIb randomized trial. *AIDS* 2010; 24: 55–65.
2. Azijn H, *et al.* TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTI-resistant HIV-1. *Antimicrob Agents Chemother* 2010; 54: 718–27.
3. Macarthur RD. Clinical Trial Report: TMC278 (Rilpivirine) versus efavirenz as initial therapy in treatment-naïve, HIV-1-infected patients. *Curr Infect Dis Rep* 2011; 13: 1–3.
4. Miller CD, *et al.* Rilpivirine: a new addition to the anti-HIV-1 armamentarium. *Drugs Today* 2011; 47: 5–15.
5. Molina JM, *et al.* Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; 378: 238–46.
6. Cohen CJ, *et al.* Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; 378: 229–37.

Adverse Effects

The most common adverse effects of moderate intensity associated with antiretroviral regimens containing rilpivirine are depressive disorders, insomnia, headache, and rashes. Depressive disorders include depressed mood, altered mood, dysphoria, and negative thoughts, and more serious psychiatric adverse effects such as severe depression, and suicidal ideation and suicide attempts. Other adverse effects of moderate intensity include abdominal pain, dry mouth, nausea and vomiting, fatigue, somnolence, abnormal dreams, and dizziness.

Raised liver enzyme values of more than 2.5 times the upper limit of normal were reported in 3 to 4% of patients. Raised total bilirubin and serum creatinine values and raised serum-cholesterol (total and low-density lipoprotein) concentrations have been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including rilpivirine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including rilpivirine.

Precautions

Rilpivirine is not recommended in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution in patients with moderate liver disease. It should also be used with caution in patients with severe renal impairment or end-stage renal disease.

Interactions

Rilpivirine is metabolised mainly by cytochrome P450 isoenzyme CYP3A4. Consequently, it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Clarithromycin, erythromycin, and troleandomycin may increase the plasma concentration of rilpivirine due to enzyme inhibition; an alternative to these macrolides (such as azithromycin) should be considered whenever possible. Alternatively, enzyme inducers may decrease plasma concentrations of rilpivirine. Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, systemic corticosteroids (except for single doses), and St John's wort may significantly decrease the concentration of rilpivirine due to CYP3A enzyme induction. Use of these drugs with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Drugs that increase the gastric pH may also decrease plasma concentrations of rilpivirine and result in possible loss of antiviral activity and development of resistance. Use of rilpivirine plus a proton pump inhibitor is contra-indicated, while antacids or histamine H_2-receptor antagonists should be used with caution and only histamine H_2-receptor antagonists that can be given once daily should be used. When given concomitantly, histamine H_2-receptor antagonists should be given at least 12 hours before or at least 4 hours after rilpivirine, while antacids should be given at least 2 hours before or at least 4 hours after rilpivirine.

Rilpivirine inhibits p-glycoprotein *in vitro* and plasma concentrations of drugs transported by this mechanism (such as digoxin and dabigatran) may be increased.

Supratherapeutic doses of rilpivirine prolong the QTc interval; consequently, caution is advised when rilpivirine is given with drugs with a known risk of torsade de pointes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Edurant; *Canad.*: Edurant; *Denm.*: Edurant; Eviplera; *Irl.*: Edurant; *Israel*: Edurant; *Jpn*: Edurant; *Neth.*: Edurant; *Norw.*: Edurant; *Spain*: Edurant; *Swed.*: Edurant; *Switz.*: Edurant; *UK*: Edurant; *USA*: Edurant.

Multi-ingredient Preparations. *Ger.*: Eviplera; *Israel*: Eviplera; *Norw.*: Eviplera; *Swed.*: Eviplera; *Switz.*: Eviplera; *UK*: Eviplera; *USA*: Complera.

Rimantadine Hydrochloride

(BANM, USAN, rINNM)

EXP-126; Hidrocloruro de rimantadina; Rimantadina, hidrocloruro de; Rimantadine, Chlorhydrate de; Rimantadini Hydrochloridum; Римантадина Гидрохлорид.
(*RS*)-1-(Adamantan-1-yl)ethylamine hydrochloride; α-Methyl-1-adamantanemethylamine hydrochloride.
$C_{12}H_{21}N$,HCl=215.8.
CAS — 13392-28-4 (rimantadine); 1501-84-4 (rimantadine hydrochloride).
ATC — J05AC02.
ATC Vet — QJ05AC02.
UNII — JEI07OOS8Y.

Pharmacopoeias. In *US*.

USP 36: (Rimantadine Hydrochloride). Store at a temperature of 15 degrees to 30 degrees.

Uses and Administration

Rimantadine hydrochloride is used similarly to amantadine hydrochloride (p. 890.3) in the prophylaxis and treatment of susceptible influenza A infections (p. 960.2). It is given orally in usual adult doses of 200 mg daily in divided doses. In elderly patients the usual daily dose is 100 mg. A dosage reduction is also necessary in patients with severe renal or severe hepatic impairment (see below).

For details of doses in children, see below.

Reviews.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/06/08).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 21/10/09).

Administration in children. For the prophylaxis of influenza A in children from 1 year of age, an oral dose of 5 mg/kg daily in 1 or 2 divided doses, up to a maximum daily dose of 150 mg, may be given. Children 10 years of age and older may be given 100 mg twice daily; those weighing less than 40 kg should be given a dose of 5 mg/kg daily, regardless of their age. Although not licensed for the treatment of influenza A some experts consider that it may be given to children from 1 year of age.

Administration in hepatic or renal impairment. The usual oral dose of rimantadine in patients with severe renal or severe hepatic impairment and in elderly nursing home patients is 100 mg daily.

Adverse Effects and Precautions

The incidence and severity of adverse effects associated with rimantadine appear to be low. Those most commonly reported are gastrointestinal disturbances such as nausea, vomiting, abdominal pain, dry mouth, and anorexia, CNS effects such as headache, insomnia, nervousness, and dizziness, and asthenia. Other less frequently reported adverse effects include ataxia, agitation, concentration difficulties, diarrhoea, dyspepsia, depression, dyspnoea, skin rash, somnolence, and tinnitus.

There have been reports of convulsions, including grand mal convulsions, and rimantadine should be given with caution to patients with epilepsy. Doses are reduced in severe renal or hepatic impairment; reduced doses are also used in the elderly.

A review[1] of clinical studies in adults concluded that rimantadine and amantadine were equally effective for prevention and treatment of influenza A, but rimantadine was significantly better tolerated than amantadine at usual doses. Another systematic review[2] evaluating the safety and efficacy of amantadine and rimantadine in children and the elderly with influenza A concluded that although rimantadine was safe in these groups, its efficacy was unproven and therefore its use could not be recommended.

In a study[3] to evaluate the safety of long-term rimantadine for elderly, chronically ill individuals during an influenza A epidemic, a significantly greater proportion of patients taking rimantadine developed anxiety and/or nausea compared with those taking placebo. There was also a significantly greater number of days in which anxiety, nausea, confusion, depression, or vomiting were reported. Most of these adverse effects lasted less than 9 days and were seldom severe except in 2 patients who withdrew from the study because of insomnia, anxiety, or both and a third who suffered a generalised convulsion. In a larger study[4] the incidence of these symptoms was similar in treatment and placebo groups.

Observations of seizures in 2 patients receiving influenza prophylaxis with rimantadine hydrochloride emphasised that chronically ill and elderly patients prone to seizures (especially those who may have had antiepileptic therapy withdrawn) may be at greater risk of developing seizures.[5] A precautionary measure of reducing the rimantadine hydrochloride dosage to 100 mg daily and temporary re-introduction of antiepileptics was suggested.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 3/10/07).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/02/08).
3. Patriarca PA, *et al.* Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A virus infections in nursing homes. *Antimicrob Agents Chemother* 1984; 26: 101–3.
4. Monto AS, *et al.* Safety and efficacy of long-term use of rimantadine for prophylaxis of type A influenza in nursing homes. *Antimicrob Agents Chemother* 1995; 39: 2224–8.
5. Bentley DW, *et al.* Rimantadine and seizures. *Ann Intern Med* 1989; 110: 323–4.

Breast feeding. Rimantadine is distributed into breast milk in *animals* in concentrations about twice those measured in the serum. US licensed product information states that rimantadine should be avoided in breast-feeding mothers.

Pregnancy. Although there are no data available on the use of rimantadine in pregnant women, US licensed product information states that it should only be used if potential benefit justifies the risk to the fetus as embryotoxicity has been reported in *rats* given high doses of rimantadine.

Antiviral Action

Rimantadine is an M2 ion channel inhibitor that inhibits influenza A virus replication mainly by blocking the M2 protein ion channel, thereby preventing fusion of the virus and the host-cell membranes and the release of viral RNA into the cytoplasm of infected cells.

Resistance to rimantadine can occur rapidly and resistant virus may be transmitted to close contacts of patients treated with rimantadine and cause influenza. Rimantadine and amantadine show complete cross-resistance.

Resistance. Resistance of influenza A viruses to the adamantane M2 ion channel inhibitors amantadine and rimantadine can occur spontaneously or emerge rapidly during treatment. A single point mutation in the code sequence for the amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross-resistance to both amantadine and rimantadine. The resistant viruses can still replicate and be transmitted.[1-3] A report[4] describing the global prevalence of adamantane-resistant influenza A viruses over a 10 year period shows an increase in drug resistance from 0.4% during the 1994/5 influenza season to 12.3% during the 2003/4 season. During the 2005/6 influenza season, WHO and the National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories in the United States reported tests on 120 influenza viruses of which 109 (91%) were found to have substitutions in the M2 protein that would confer resistance to amantadine and rimantadine.[3] In the USA, the reported adamantane resistance rate for influenza A increased from 11% for the 2004/5 influenza season to 92% for the 2005/6 influenza season.[5] On the basis of this information, the CDC no longer recommends amantadine or rimantadine for the treatment or prophylaxis of influenza A infections.[3,6]

1. Belshe RB, *et al.* Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. *J Virol* 1988; 62: 1508–12.
2. Hayden FG, *et al.* Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med* 1989; 321: 1696–1702.
3. CDC. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005–06 influenza season. *MMWR* 2006; 55: 44–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5502a7.htm (accessed 13/06/08)
4. Bright RA, *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; 366: 1175–81.
5. Bright RA, *et al.* Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. *JAMA* 2006; 295: 891–4.
6. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; 56 (RR-6): 1–54. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf (accessed 13/06/08)

Pharmacokinetics

Rimantadine hydrochloride is well, but slowly, absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 6 hours. It has a large volume of distribution and long elimination half-life; reported figures for half-life in healthy adults range from 13 to 65 hours (mean 25.4 hours) and from 20 to 65 hours (mean 32 hours) in those over 70 years of age. Protein binding of rimantadine is about 40%. It is extensively metabolised in the liver with less than 25% of a dose being excreted unchanged in the urine; about 75% is excreted as hydroxylated metabolites over 72 hours. In severe renal or hepatic impairment the elimination half-life is about double, necessitating a dosage reduction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Jin Di Na (金迪纳); Jin-Tong (津彤); Li An (立安); Tai Zhi Ao (太之奥); *Cz.*: Maridin†; *Mex.*: Gabirol; *Pol.*: Rimantin; *Rus.*: Algirem (Альгирем)†; Orvirem (Орвирем); *Ukr.*: Remavir (Ремавир); *USA*: Flumadine.

Multi-ingredient Preparations. *Rus.*: Antigrippin-Maximum (Антигриппин-Максимум); Antigrippin-Maximum (Антигриппин-Максимум).

Pharmacopoeial Preparations
USP 36: Rimantadine Hydrochloride Tablets.

Ritonavir *(BAN, USAN, rINN)*

A-84538; Abbott-84538; ABT-538; Ritonavilin; Ritonavirum; Ритонавир.

5-Thiazolylmethyl [(αS)-α-[(1S,3S)-1-hydroxy-3-((2S)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido)-4-phenylbutyl]phenethyl]carbamate; *N*-[(1S,3S,4S)-1-Benzyl-3-hydroxy-5-phenyl-4-(1,3-thiazol-5-ylmethoxycarbonylamino)pentyl]-*N*′-[(2-isopropyl-1,3-thiazol-4-yl)methyl](methyl)carbamoyl]-L-valinamide.

$C_{37}H_{48}N_6O_5S_2$=720.9

CAS — 155213-67-5.

ATC — J05AE03.

ATC Vet — QJ05AE03.

UNII — O3J8G9O825.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Ritonavir). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane; very slightly soluble in acetonitrile. It exhibits polymorphism. Protect from light.

USP 36: (Ritonavir). A white to light tan powder. Practically insoluble in water; very soluble in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature between 5 degrees and 30 degrees. Protect from light.

Uses and Administration

Ritonavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when ritonavir is used alone, and it is therefore given with other antiretrovirals. It is also widely used as a pharmacokinetic enhancer of other HIV-protease inhibitors (ritonavir-boosted therapy).

For treatment, ritonavir is given orally in an adult dose of 600 mg twice daily with food. In order to minimise nausea, ritonavir may be started at a dose of 300 mg twice daily and gradually increased over a period of up to 14 days by 100 mg twice daily to a total of 600 mg twice daily. For details of doses in children, see below.

When used as a pharmacokinetic enhancer ritonavir is given in doses of 100 to 200 mg once or twice daily.

Reviews.
1. Lea AP, Faulds D. Ritonavir. *Drugs* 1996; 52: 541–6.
2. Cooper CL, *et al.* A review of low-dose ritonavir in protease inhibitor combination therapy. *Clin Infect Dis* 2003; 36: 1585–92.
3. Wilkins E. The current role of ritonavir-boosted protease inhibitors in the management of HIV infection. *J HIV Ther* 2008; 13: 9–18.
4. Bierman WF, *et al.* HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS* 2009; 23: 279–91.

Administration. Adjusting the dosage of ritonavir from 600 mg twice daily to 300 mg every 6 hours improved tolerability in 2 patients who would otherwise have stopped the drug.[1]

1. Merry C, *et al.* Improved tolerability of ritonavir derived from pharmacokinetic principles. *Br J Clin Pharmacol* 1996; 42: 787.

Administration in children. For the treatment of HIV infection in children, ritonavir is given daily with other antiretroviral drugs. US licensed product information permits the use of oral ritonavir in infants over 1 month of age, whereas in the UK it is recommended from 2 years of age. The dose given should not exceed the maximum adult dose of 600 mg twice daily.

The recommended dose regimen is an initial dose of 250 mg/m^2 twice daily increasing by 50 mg/m^2 twice daily at 2- or 3-day intervals up to 350 to 400 mg/m^2 twice daily.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing ritonavir are asthenia, gastrointestinal effects (abdominal pain, anorexia, nausea, vomiting, and particularly diarrhoea), headache, taste disorder, and numbness or tingling around the mouth or in the extremities. One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Other commonly reported adverse effects include anxiety, dizziness, insomnia, fever, other gastrointestinal effects (dry mouth, dyspepsia, flatulence, local throat irritation, mouth ulcer), hyperaesthesia, malaise, pharyngitis, pruritus, rash, sweating, vasodilatation, and weight loss. Allergic reactions include urticaria, mild skin eruptions, bronchospasm, angioedema, and rarely anaphylaxis. A possible association with Stevens-Johnson syndrome has been reported with ritonavir. Reported abnormal laboratory results are decreased haemoglobin levels and potassium concentrations, increased eosinophil counts, raised liver enzymes, amylase, and uric acid concentrations, and decreased free and total thyroxine concentrations; white blood cell and neutrophil counts may be reduced or increased.

Adverse effects associated with the use of ritonavir as a pharmacokinetic booster are dependent on the other HIV-protease inhibitor.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including ritonavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy including ritonavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Ritonavir (as an antiviral agent or as a pharmacokinetic enhancer) should not be used in patients with decompensated liver disease. Caution is advised in patients with severe hepatic impairment (Child-Pugh Grade C) without decompensation, when ritonavir is used as a pharmacokinetic booster with another HIV-protease inhibitor, although specific recommendations depend on the other drug. Patients with pre-existing liver disease or co-infection with chronic hepatitis B or C who are treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Patients should be monitored for signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, and increased serum lipase or amylase levels) and ritonavir treatment should be stopped in patients developing pancreatitis. Ritonavir may prolong the PR interval in some patients, in rare cases leading to second- or third-degree AV block; it should therefore be used with caution in those at increased risk, including patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischaemic heart disease, or cardiomyopathy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ritonavir as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

The interaction of ritonavir with the cytochrome P450 isoenzyme system is complex. Ritonavir is metabolised mainly by CYP3A4 (and to a lesser extent 2D6), and it also strongly **inhibits** these and other isoenzymes in the following rank order:

CYP3A > CYP2D6 > CYP2C9 > CYP2C19 > CYP2A6, CYP2E1

Conversely, ritonavir also **induces** the activity of some isoenzymes, including CYP1A2, CYP2C9, and CYP2C19.

Consequently, use with ritonavir may lead to altered serum concentrations of drugs metabolised by these enzymes. The enzyme-inhibiting properties of ritonavir are exploited in its use as a pharmacokinetic enhancer to boost other HIV-protease inhibitors.

In addition to its effects on the cytochrome P450 isoenzyme system, ritonavir has a high affinity for P-glycoprotein, of which it is both a substrate, and a strong inhibitor. Ritonavir also induces the activity of glucuronosyltransferases (UGT).

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir with drugs for which elevated plasma concentrations caused by ritonavir-mediated enzyme inhibition may lead to serious or life-threatening events. In the USA, such drugs include:
- the alpha$_1$-adrenergic antagonist alfuzosin
- antiarrhythmics (amiodarone, bepridil, flecainide, propafenone, and quinidine)
- antipsychotics (clozapine and pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (lovastatin and simvastatin)

For similar reasons, UK licensed product information also contra-indicates the use of ritonavir with the analgesics pethidine, piroxicam, and dextropropoxyphene, the antiarrhythmic encainide, the antihistamines astemizole and terfenadine, the antibacterial fusidic acid, and some other sedatives and hypnotics (clorazepate, diazepam, estazolam, and flurazepam). Use of rifabutin is also contra-indicated in the UK when ritonavir is being used in antiretroviral doses of 600 mg twice daily, although it may be used in adjusted doses when low-dose ritonavir is used to boost selected HIV-protease inhibitors (see under Uses and Administration of Rifabutin, p. 349.1).

Owing to the potential for increased serum concentrations of sildenafil, licensing authorities contra-indicate ritonavir with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir may increase serum concentrations of inhaled fluticasone or salmeterol and combination with either is not

recommended. Ritonavir is not recommended for use with voriconazole as substantially reduced plasma concentrations of the latter drug may occur; when ritonavir doses of 400 mg twice daily or higher are used co-administration is contra-indicated. St John's wort decreases the concentration of ritonavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Ritonavir should be used with caution with other drugs that can cause PR-interval prolongation (such as calcium-channel blockers, beta blockers, digoxin, and atazanavir), particularly where those drugs are also metabolised by CYP3A4.

Oral liquid formulations of ritonavir currently contain alcohol and use with disulfiram or metronidazole should be avoided.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

References.

1. Foisy MM, *et al.* Induction effects of ritonavir: implications for drug interactions. *Ann Pharmacother* 2008; 42: 1048–59.

Antiviral Action

Ritonavir is a selective, competitive, reversible inhibitor of HIV protease. It is active against HIV-1 and, to a lesser extent, HIV-2. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Ritonavir is also a potent inhibitor of the cytochrome P450 subfamily CYP3A (chiefly the isoenzyme CYP3A4), and low-dose ritonavir is used with other HIV-protease inhibitors to decrease their metabolism and thus increase plasma concentrations of the other HIV-protease inhibitor; such use is referred to as ritonavir pharmacokinetic enhancement or ritonavir-boosted therapy. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur; in general the greater the number of mutations, the higher the level of resistance. Cross-resistance between HIV-protease inhibitors and NRTIs or NNRTIs is considered unlikely.

Pharmacokinetics

Ritonavir is absorbed after oral doses and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food, and is dose-related. Protein binding is reported to be about 98% and penetration into the CNS is minimal. Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Five metabolites have been identified and the major metabolite has antiviral activity, but concentrations in plasma are low. Studies in HIV-infected children 2 to 14 years of age indicate that ritonavir clearance is 1.5 to 1.7 times greater than in adults. About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine (3.5% as unchanged drug). The elimination half-life is 3 to 5 hours.

References.

1. Hsu A, *et al.* Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* 1997; 41: 898–905.
2. Hsu A, *et al.* Ritonavir: clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; 35: 275–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Busvir; Rifaxit†; *Austral.*: Norvir; *Austria*: Norvir; *Belg.*: Norvir; *Braz.*: Norvir; Ritovir; *Canad.*: Norvir; *Chile*: Norvir; *China*: Norvir (爱泊威); *Cz.*: Norvir; *Denm.*: Norvir; *Fin.*: Norvir; *Fr.*: Norvir; *Ger.*: Norvir; *Gr.*: Norvir; *Hong Kong*: Norvir; *Hung.*: Norvir; *India*: Empetus; Ritomune; *Indon.*: Norvir; *Irl.*: Norvir; *Israel*: Norvir; *Ital.*: Norvir; *Jpn*: Norvir; *Malaysia*: Norvir; *Mex.*: Norvir; *Neth.*: Norvir; *Norw.*: Norvir; *NZ*: Norvir; *Pol.*: Norvir; *Port.*: Norvir; *Rus.*: Norvir (Норвир); *S.Afr.*: Norvir; *Singapore*: Norvir; *Spain*: Norvir; *Swed.*: Norvir; *Switz.*: Norvir; *Thai.*: Norvir; Rinavir†; *Turk.*: Norvir; *UK*: Norvir; *USA*: Norvir; *Venez.*: Norvir.

Multi-ingredient Preparations. *Arg.*: Kaletra; *Austral.*: Kaletra; *Austria*: Kaletra; *Belg.*: Kaletra; *Braz.*: Kaletra; *Canad.*: Kaletra; *Chile*: Kaletra; *China*: Aluvia (克力芝); *Cz.*: Kaletra; *Denm.*: Kaletra; *Fin.*: Kaletra; *Fr.*: Kaletra; *Ger.*: Kaletra; *Gr.*: Kaletra; *Hong Kong*: Kaletra; *Hung.*: Kaletra; *India*: Emletra; Lopimune; Ritomax-L; *Irl.*: Kaletra; *Israel*: Kaletra; *Ital.*: Kaletra; *Malaysia*: Kaletra; *Mex.*: Kaletra; *Neth.*: Kaletra; *Norw.*: Kaletra; *NZ*: Kaletra; *Pol.*: Kaletra; *Port.*: Kaletra; *Rus.*: Kaletra (Калетра); *S. Afr.*: Aluvia; Kaletra; *Singapore*: Kaletra; *Spain*: Kaletra; *Swed.*: Kaletra; *Switz.*: Kaletra; *Thai.*: Aluvia; Kaletra; *Turk.*: Kaletra; *UK*: Kaletra; *USA*: Kaletra; *Venez.*: Kaletra.

Pharmacopoeial Preparations

USP 36: Lopinavir and Ritonavir Tablets; Ritonavir Capsules; Ritonavir Oral Solution; Ritonavir Tablets.

Saquinavir *(BAN, USAN, rINN)*

Ro-31-8959; Sakinavir; Saquinavirum; Саквинавир.

N^1-[(1*S*,2*R*)-1-Benzyl-3-[(3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)perhydroisoquinolin-2-yl]-2-hydroxypropyl]-N^2-(2-quinolylcarbonyl)-L-aspartamide; (*S*)-*N*-[(α*S*)-α-[(1*R*)-2-[(3*S*,4a*S*,8a*S*)-3-(*tert*-Butylcarbamoyl)octahydro-2(1*H*)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamidosuccinamide.

$C_{38}H_{50}N_6O_5$=670.9

CAS — 127779-20-8.

ATC — J05AE01.

ATC Vet — QJ05AE01.

UNII — L3JE09KZ2F.

Pharmacopoeias. In *Int.*

Saquinavir Mesilate *(BANM, rINNM)*

Mesilato de saquinavir; Ro-31-8959/003; Sakinaviirimesilaatti; Sakinavirmesilat; Saquinavir, Mésilate de; Saquinavir, mesilato de; Saquinavir Mesylate (USAN); Saquinaviri Mesilas; Saquinavirmesilat; Саквинавира Мезилат.

Saquinavir methanesulfonate.

$C_{38}H_{50}N_6O_5.CH_4O_3S$=767.0

CAS — 149845-06-7.

ATC — J05AE01.

ATC Vet — QJ05AE01.

UNII — UHB9Z3841A.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Saquinavir Mesilate). A white or almost white, slightly hygroscopic powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Saquinavir Mesylate). Store in airtight containers.

Uses and Administration

Saquinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when saquinavir is used alone, and it is therefore used with other antiretrovirals, including low-dose ritonavir which is given as a pharmacokinetic enhancer (ritonavir-boosted saquinavir).

Saquinavir is given orally as the mesilate but doses are expressed in terms of the base; 229 mg of saquinavir mesilate is equivalent to about 200 mg of saquinavir. The dose is 1 g twice daily given with ritonavir 100 mg twice daily with or after food.

To reduce the risk of cardiac conduction disturbances (see below), UK licensed product information advises that treatment-naive patients be given a reduced dose of 500 mg twice daily (with ritonavir 100 mg twice daily) for the first 7 days of treatment. Patients switching immediately (without a wash-out period) from another ritonavir-boosted HIV-protease inhibitor or a NNRTI-based regimen, however, should start saquinavir at the standard recommended dose.

Reviews.

1. Vella S, Floridia M. Saquinavir: clinical pharmacology and efficacy. *Clin Pharmacokinet* 1998; 34: 189–201.
2. Piggin DP, Plosker GL. Saquinavir soft-gel capsule: an updated review of its use in the management of HIV infection. *Drugs* 2000; 60: 481–516.
3. Plosker GL, Scott LJ. Saquinavir: a review of its use in boosted regimens for treating HIV infection. *Drugs* 2003; 63: 1299–1324.
4. la Porte CJ. Saquinavir, the pioneer antiretroviral protease inhibitor. *Expert Opin Drug Metab Toxicol* 2009; 5: 1313–22.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing saquinavir are gastrointestinal disorders (abdominal pain, diarrhoea, flatulence, nausea, vomiting) and fatigue. Other commonly reported adverse effects include alopecia, anaemia, anorexia, increased appetite, asthenia, constipation, dizziness, dry lips, mouth and skin, dyspepsia, dyspnoea, eczema, headache, hypersensitivity, decreased libido, malaise, muscle spasm, paraesthesia, peripheral neuropathy, pruritus, rash, sleep disturbances, and taste disorders. Commonly reported laboratory abnormalities include raised liver enzyme values, increased blood amylase, bilirubin, and creatinine, and lowered haemoglobin and platelet, lymphocyte, and white blood cell count. Rare but serious adverse effects that may be associated with saquinavir include acute myeloid leukaemia, haemolytic anaemia, allergic reactions, ascites, bullous skin eruptions, intestinal obstruction, jaundice, nephrolithiasis, pancreatitis, polyarthritis, portal hypertension, seizures, Stevens-Johnson syndrome, attempted suicide, and thrombocytopenia (occasionally fatal). Ritonavir-boosted saquinavir may cause dose-dependent prolongation of both the PR and QT intervals; cases of second- or third-degree AV block and torsade de pointes have been reported rarely.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including saquinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including saquinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Precautions

Ritonavir-boosted saquinavir should not be used in patients with decompensated liver disease and should be used with caution in patients with moderate hepatic or severe renal impairment. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Ritonavir-boosted saquinavir may cause cardiac conduction abnormalities and is therefore best avoided in patients at increased risk, such as those with underlying structural heart disease (including congestive heart failure and other cardiomyopathies), pre-existing cardiac conduction abnormalities (including QT-interval prolongation, clinically significant bradycardia, or AV block), ischaemic heart disease, or uncorrected electrolyte disturbances (particularly hypokalaemia). Baseline and follow-up electrocardiograms should be considered for patients starting ritonavir-boosted saquinavir, particularly when use cannot be avoided in those at high risk for conduction disturbances, or where hepatic impairment or drug interactions (see below) may increase exposure to saquinavir; treatment should be stopped if arrhythmia, or prolongation of the PR or QT intervals occur. Treatment-naive patients are considered to be at particular risk of QT-and PR-interval prolongation, with the highest risk occurring in the first week of therapy; UK licensed product information therefore recommends a lower initial dose for the first week of treatment in these patients (see above).

For information on the use of HIV-protease inhibitors in pregnancy, see under Indinavir, p. 987.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies saquinavir as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Saquinavir is reported to be metabolised by the cytochrome P450 system, with the specific isoenzyme CYP3A4 responsible for more than 90% of the hepatic metabolism. Saquinavir is also a substrate and an inhibitor of P-glycoprotein. Drugs that affect this isoenzyme and/or P-glycoprotein may modify saquinavir plasma concentrations. Saquinavir may alter the pharmacokinetics of other drugs that are metabolised by this enzyme system or that are substrates for P-glycoprotein.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted saquinavir with drugs that are highly dependent on CYP3A4 or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. In the UK, these drugs may include

- antiarrhythmics (amiodarone, bepridil, dofetilide, disopyramide, flecainide, hydroquinidine, systemic lidocaine, propafenone, and quinidine)
- antidepressants (amitriptyline, imipramine, and trazodone)
- antihistamines (astemizole, mizolastine, and terfenadine)
- the antimalarial quinine
- antimycobacterials (dapsone and rifampicin)
- antipsychotics (pimozide)
- macrolide antibacterials (erythromycin and clarithromycin)

- opioid analgesics (alfentanil, fentanyl, and methadone)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated.

Although UK licensed product information contra-indicates the use of phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil) with ritonavir-boosted saquinavir, other authorities consider that these combinations may be used with caution, with adjusted doses, in certain clinical situations (see Uses and Administration of Sildenafil, p. 2364.2, Tadalafil, p. 2368.2, and Vardenafil, p. 2372.1). Ritonavir-boosted saquinavir may also increase serum concentrations of inhaled fluticasone or salmeterol and combination with either is not recommended. Both Garlic and St John's wort decrease the concentration of saquinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

Use of ritonavir-boosted saquinavir is best avoided with drugs known to prolong the QT or PR interval (such as ibutilide, sotalol, halofantrine, pentamidine, sparfloxacin, clozapine, haloperidol, the phenothiazines, sertindole, sultopride, ziprasidone, atazanavir, ritonavir-boosted lopinavir, digoxin, the calcium-channel blockers, and the beta-adrenergic blockers). Where such combinations cannot be avoided, US licensed product information advises that they may be used with caution and ECG monitoring. Use with drugs that both prolong the QT interval and increase serum concentrations of saquinavir is contra-indicated.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Saquinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. HIV isolates resistant to saquinavir have been reported and variable cross-resistance with other HIV-protease inhibitors has been seen. Cross-resistance between saquinavir and NRTIs or NNRTIs is unlikely because these drugs have different target enzymes.

Pharmacokinetics

Saquinavir is absorbed to a limited extent (about 30%) after oral doses of the mesilate and undergoes extensive first-pass hepatic metabolism, resulting in a bioavailability of 4% when taken with food. Bioavailability was found to be greater from a soft gelatin capsule formulation of saquinavir base in a suitable vehicle (*Fortovase, Roche*) than from a hard capsule formulation (*Invirase, Roche*). Bioavailability is substantially less when saquinavir is taken in the fasting state. Plasma concentrations are reported to be higher in HIV-infected patients than in healthy subjects. Saquinavir is about 98% bound to plasma proteins and extensively distributed into the tissues, although CSF concentrations are reported to be negligible. It is rapidly metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to several inactive monohydroxylated and dihydroxylated compounds. It is excreted mainly in the faeces with a reported terminal elimination half-life of 13.2 hours.

References.
1. Regazzi MB, *et al.* Pharmacokinetic variability and strategy for therapeutic drug monitoring of saquinavir (SQV) in HIV-1 infected individuals. *Br J Clin Pharmacol* 1999; 47: 379–82.
2. Grub S, *et al.* Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2002; 71: 122–30.
3. Acosta EP, *et al.* Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; 48: 430–6.
4. Dickinson L, *et al.* Population pharmacokinetics of ritonavir-boosted saquinavir regimens in HIV-infected individuals. *J Antimicrob Chemother* 2008; 62: 1344–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fortovase; Proteovir; *Austral.*: Fortovase†; Invirase; *Austria*: Invirase; *Belg.*: Invirase; *Braz.*: Fortovase; Invirase; Svir; *Canad.*: Invirase; *Chile*: Invirase; *China*: Fortovase (复得维); Invirase (因凝富); *Cz.*: Invirase; *Denm.*: Invirase; *Fin.*: Invirase; *Fr.*: Invirase; *Ger.*: Invirase; *Gr.*: Fortovase; Invirase; *Hong Kong*: Invirase; *Hung.*: Invirase; *Irl.*: Invirase; *Israel*: Invirase; *Ital.*: Invirase; *Jpn*: Fortovase†; Invirase; *Malaysia*: Invirase; *Mex.*: Fortovase; Invirase; *Neth.*: Fortovase†; Invirase; *Norw.*: Invirase; *NZ*: Fortovase†; Invirase†; *Philipp.*: Invirase; *Pol.*: Invirase; *Port.*: Invirase; *Rus.*: Fortovase (Фортоваза); Invirase (Инвираза); *S.Afr.*: Invirase; *Singapore*: Fortovase; Invirase; *Spain*: Invirase; *Swed.*: Invirase; *Switz.*: Invirase; *Thai.*: Fortovase†; Invirase; *UK*: Invirase; *USA*: Invirase; *Venez.*: Fortovase.

Pharmacopoeial Preparations
USP 36: Saquinavir Capsules.

Simeprevir *(USAN, pINN)*

Siméprévir; Simeprevirum; TMC-435; TMC-435350; Симепревир.

(2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(Cyclopropylsulfonyl)-2-({7-methoxy-8-methyl-2-[4-(1-methylethyl)thiazol-2-yl]quinolin-4-yl}oxy)-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide.

$C_{38}H_{47}N_5O_7S_2$=749.9

CAS — 923604-59-5.

UNII — 9WSSRD66HZ.

Profile

Simeprevir is an oral HCV-protease inhibitor effective against hepatitis C virus (HCV) serine protease NS3/4A. It is used in the treatment of chronic hepatitis C (p. 952.1) genotype 1 infection in adults with compensated liver disease, including cirrhosis. Doses are given as the sodium salt but expressed as the base; simeprevir 150 mg is equivalent to about 154 mg of simeprevir sodium. An oral dose equivalent to simeprevir 150 mg once daily with food is given as part of a combined regimen with peginterferon alfa and ribavirin (tri-therapy) for 12 weeks. This is followed by 12 or 36 weeks of treatment with peginterferon alfa and ribavirin (bi-therapy) depending on patient history and hepatitis C-RNA (HCV-RNA) levels.

References.
1. Vaidya A, Perry CM. Simeprevir: first global approval. *Drugs* 2013; 73: 2093–2106.
2. You DM, Pockros PJ. Simeprevir for the treatment of chronic hepatitis C. *Expert Opin Pharmacother* 2013; 14: 2581–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Galexos; *Jpn*: Sovriad; *USA*: Olysio.

Sofosbuvir *(USAN, rINN)*

PSI-7977; Sofosbuvirum; Софосбувир.

1-Methylethyl *N*-[(*S*)-[[(2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl]methoxy]phenoxyphosphoryl]-L-alaninate.

$C_{22}H_{29}FN_3O_9P$=529.5

CAS — 1190307-88-0.

UNII — WJ6CA3ZU8B.

Profile

Sofosbuvir is an oral nucleotide analogue inhibitor effective against hepatitis C virus (HCV) polymerase NS5B. It is used in the treatment of chronic hepatitis C (p. 952.1) genotypes 1, 2, 3, or 4. Sofosbuvir is given in an oral dose of 400 mg once daily in a combined regimen according to genotype:

- 1 or 4: sofosbuvir with ribavirin and peginterferon alfa for 12 weeks. Sofosbuvir with ribavirin for 24 weeks may be used in patients with genotype 1 infection who are unable to take peginterferon alfa
- 2: sofosbuvir with ribavirin for 12 weeks
- 3: sofosbuvir with ribavirin for 24 weeks

It has also been tried in combination with daclatasvir (p. 971.1).

References.
1. Herbst DA, Reddy KR. Sofosbuvir, a nucleotide polymerase inhibitor, for the treatment of chronic hepatitis C virus infection. *Expert Opin Invest Drugs* 2013; 22: 527–36.
2. Asselah T. Sofosbuvir for the treatment of hepatitis C virus. *Expert Opin Pharmacother* 2014; 15: 121–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Sovaldi.

Sorivudine *(BAN, USAN, rINN)*

Bravavir; Bromovinylarauracil; Brovavir; BV-araU; BVAU; Sorivudin; Sorivudina; Sorivudinum; SQ-32756; YN-72; Соривудин.

(*E*)-1-β-D-Arabinofuranosyl-5-(2-bromovinyl)uracil.

$C_{11}H_{13}BrN_2O_6$=349.1

CAS — 77181-69-2.

UNII — C7VOZ162LV.

Profile

Sorivudine is a synthetic thymidine derivative with antiviral activity against varicella-zoster virus. An oral preparation has been given for the treatment of herpes zoster but was withdrawn from the market in Japan after deaths in patients also given fluorouracil. A topical preparation is now being studied.

References.
1. Yawata M. Deaths due to drug interaction. *Lancet* 1993; 342: 1166.
2. Diasio RB. Sorivudine and 5-fluorouracil: a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; 46: 1–4.

Stavudine *(BAN, USAN, pINN)*

BMY-27857; d4T; Estavudina; Sanilvudine; Stavudiini; Stavudin; Stavudinas; Stavudinum; Ставудин.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine.

$C_{10}H_{12}N_2O_4$=224.2

CAS — 3056-17-5.

ATC — J05AF04.

ATC Vet — QJ05AF04.

UNII — BO9LE4QFZF.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Stavudine). A white or almost white powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. Protect from light and humidity.

USP 36: (Stavudine). A white to off-white, crystalline powder. Soluble in water, in dimethylacetamide, and in dimethyl sulfoxide; sparingly soluble in alcohol, in acetonitrile, and in methyl alcohol; slightly soluble in dichloromethane; insoluble in petroleum spirit. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Stavudine is a nucleoside reverse transcriptase inhibitor related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when stavudine is used alone, and it is therefore used with other antiretrovirals. Stavudine is given orally, usually as a capsule or solution. Usual adult doses of stavudine are 40 mg every 12 hours for patients weighing 60 kg or more or 30 mg every 12 hours for patients weighing less than 60 kg.

For details of doses in infants, children, and adolescents, see below.

For details of reduced doses of stavudine to be used in patients with renal impairment, see below.

Reviews.
1. Hurst M, Noble S. Stavudine: an update of its use in the treatment of HIV infection. *Drugs* 1999; 58: 919–49.
2. Cheer SM, Goa KL. Stavudine once daily. *Drugs* 2002; 62: 2667–74.
3. Hill A, *et al.* Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. *Expert Opin Pharmacother* 2007; 8: 679–88.
4. Makinson A, *et al.* Safety of stavudine in the treatment of HIV infection with a special focus on resource-limited settings. *Expert Opin Drug Safety* 2008; 7: 283–93.
5. Martin JC, *et al.* Early nucleoside reverse transcriptase inhibitors for the treatment of HIV: a brief history of stavudine (D4T) and its comparison with other dideoxynucleosides. *Antiviral Ret* 2010; 85: 34–8.
6. Spaulding A, *et al.* Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naive individuals. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 10/08/10).

Administration in children. For the treatment of HIV infection in infants, children, and adolescents stavudine is given orally with other antiretroviral drugs. Doses are based on age and body-weight:

- in neonates from birth to 13 days old a dose of 500 micrograms/kg every 12 hours may be given
- in infants at least 14 days old and those weighing less than 30 kg the dose is 1 mg/kg every 12 hours
- in children and adolescents weighing 30 kg or more, the adult dose is given (see above)

Administration in renal impairment. Dosage reduction according to creatinine clearance (CC) is recommended for patients receiving oral stavudine who have renal impairment:

- CC 26 to 50 mL/minute: 20 mg every 12 hours (those weighing 60 kg or more) or 15 mg every 12 hours (those weighing less than 60 kg)
- CC below 26 mL/minute: 20 mg every 24 hours (those weighing 60 kg or more) or 15 mg every 24 hours (those weighing less than 60 kg)

Adverse Effects

The most common adverse effect reported with stavudine either as monotherapy or with other antiretrovirals is

peripheral neuropathy; risk generally relates to cumulative dose and it is also increased in patients taking stavudine with didanosine and hydroxycarbamide. Other common adverse effects include abnormal dreams, abdominal pain, nausea, diarrhoea, drowsiness, dyspepsia, fatigue, dizziness, depression, headache, insomnia, pruritus, and rash. Abnormal liver function tests may occur and hepatitis, hepatic failure, and pancreatitis have been reported rarely; fatalities have occurred and were reported most often in patients taking stavudine with didanosine and hydroxycarbamide. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs, and particularly with stavudine. There have been reports of motor weakness associated with stavudine, occurring particularly with lactic acidosis; the presentation may mimic that of *Guillain-Barré syndrome* (including respiratory failure), and symptoms may continue or worsen even after stavudine is stopped.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including stavudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including stavudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported; effects on blood lipids and fat distribution, in particular, are generally thought to occur more frequently with stavudine than with other NRTIs. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the nervous system. Peripheral neuropathy is a well recognised adverse effect of stavudine and has been the subject of a review.[1] A cross-sectional study[2] of 294 HIV-infected patients using stavudine, found increased age and height to be independently associated with development of neuropathy; the authors suggested that, where possible, patients aged at least 40 years or those who are at least 170 cm tall (and particularly those meeting both criteria) should not be treated with stavudine-based regimen.

1. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998; 19: 481–94.
2. Cherry CL, *et al.* Age and height predict neuropathy risk in patients with HIV prescribed stavudine. *Neurology* 2009; 73: 315–20.

Gynaecomastia. Bilateral gynaecomastia was associated with stavudine use in a patient with HIV infection who was also receiving lamivudine and co-trimoxazole.[1] Symptoms resolved when stavudine was stopped. Four other cases of gynaecomastia were reported in HIV-infected patients given HAART regimens containing stavudine.[2]

1. Melbourne KM, *et al.* Gynecomastia with stavudine treatment in an HIV-positive patient. *Ann Pharmacother* 1998; 32: 1108.
2. Manfredi R, *et al.* Gynecomastia associated with highly active antiretroviral therapy. *Ann Pharmacother* 2001; 35: 438–9.

Precautions

Stavudine should be used with caution in patients with a history of peripheral neuropathy; if it develops during stavudine use, the patient should be switched to an alternative treatment regimen. Treatment with stavudine may be associated with lactic acidosis and should also be stopped if there is a rapid increase in aminotransferase concentrations, pronounced hepatotoxicity (which may include progressive hepatomegaly or steatosis), or metabolic or lactic acidosis of unknown aetiology. Stavudine should be given with caution to patients (particularly obese women) with hepatomegaly, hepatitis, or other risk factors for liver disease. If liver enzymes increase to >5 times the upper limit of normal during treatment then stavudine should be stopped. Patients co-infected with chronic hepatitis B or C who are being treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. Patients with a history of, or risk factors for, pancreatitis should also be observed carefully for signs of pancreatitis during stavudine treatment. Use with other drugs likely to cause peripheral neuropathy or pancreatitis should be avoided if possible. Stavudine should be used with caution and doses reduced in patients with renal impairment.

After a 2010 regulatory review of stavudine where its benefit-risk ratio was scrutinised, the European Medicines Agency recommended that its use be strictly limited. It advised that, due to the toxicity of stavudine, the drug should only be used when no other appropriate treatments were available; patients using stavudine should be assessed frequently and switched to an appropriate alternative as soon as possible.[1]

1. EMEA. Questions and answers on the review of Zerit (stavudine): outcome of a renewal procedure (issued 17 Feb 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/human/000110/WC500102227.pdf (accessed 06/04/11)

Gender. In a prospective study[1] in a cohort of 559 Ugandan patients starting antiretroviral therapy, about a quarter changed their treatment regimen at least once over 3 years. The cause of treatment substitution was drug toxicity in 91 patients and in 76 this was due to stavudine. Analysis indicated that stavudine toxicity leading to change of regimen was almost twice as likely in women as in men, suggesting that long-term stavudine use was less well tolerated in women, and should be avoided if possible.

1. Castelnuovo B, *et al.* Stavudine toxicity in women is the main reason for treatment change in a 3-year prospective cohort of adult patients started on first-line antiretroviral treatment in Uganda. *J Acquir Immune Defic Syndr* 2011; 56: 59–63.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies stavudine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

The intracellular activation of stavudine and hence its antiviral effect may be inhibited by zidovudine, doxorubicin, and ribavirin.

Use of stavudine with other drugs known to cause pancreatitis or peripheral neuropathy should be avoided if possible. The combination of hydroxycarbamide and didanosine if given with stavudine, may carry a higher risk of adverse effects including hepatotoxicity, peripheral neuropathy, and pancreatitis (fatal and non-fatal).

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; 37: 315–16.

Phenylpropanolamine. Hypertensive crisis associated with use of phenylpropanolamine and clemastine occurred in a patient receiving HIV prophylaxis with indinavir, lamivudine, and stavudine.[1] The most likely cause was an interaction between phenylpropanolamine and stavudine, although interactions with the other antiretrovirals could not be ruled out.

1. Khurana V, *et al.* Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; 106: 118–19.

Antiviral Action

Stavudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Stavudine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Stavudine is absorbed rapidly after oral doses and peak plasma concentrations occur within 1 hour. It has a reported bioavailability of about 86%. Food delays but does not reduce absorption. Stavudine crosses the blood-brain barrier producing a CSF to plasma ratio of about 0.4 after 4 hours. Binding to plasma proteins is negligible. Stavudine is metabolised intracellularly to the active antiviral triphosphate. The elimination half-life is reported to be about 1 to 1.5 hours after single or multiple doses. The intracellular half-life of stavudine triphosphate has been estimated to be 3.5 hours *in vitro*. About 40% of a dose is excreted in the urine by active tubular secretion and glomerular filtration. Stavudine is removed by haemodialysis.

References.

1. Rana KZ, Dudley MN. Clinical pharmacokinetics of stavudine. *Clin Pharmacokinet* 1997; 33: 276–84.
2. Kaul S, *et al.* Effect of food on bioavailability of stavudine in subjects with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1998; 42: 2295–8.
3. Grasela DM, *et al.* Pharmacokinetics of single-dose oral stavudine in subjects with renal impairment and in subjects requiring hemodialysis. *Antimicrob Agents Chemother* 2000; 44: 2149–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lion; Stamar; Stavubergen; STV; Tonavir; Zerit; *Austral.*: Zerit; *Austria*: Zerit; *Belg.*: Zerit; *Braz.*: Svudin; Zeritavir†; *Canad.*: Zerit; *Chile*: Zerit; *China*: Ai Fu Ding (艾复定); Sazi (沙之); Xin Fu Da (欣复达); Zerit (赛瑞特); *Cz.*: Zerit; *Denm.*: Zerit; *Fin.*: Zerit; *Fr.*: Zerit; *Ger.*: Zerit; *Gr.*: Zerit; *Hong Kong*: Zerit; *Hung.*: Zerit; *India*: Stavir; *Indon.*: Zerit†; *Irl.*: Zerit; *Ital.*: Zerit; *Jpn*: Zerit; *Malaysia*: Virostav; *Mex.*: Landstav†; Pravidine†; Ranstar†; Zerit; *Neth.*: Zerit; *Norw.*: Zerit†; *NZ*: Zerit; *Pol.*: Zerit; *Port.*: Zerit; *Rus.*: Actastav (Актастав); Zerit (Зерит); *S.Afr.*: Stavir; Vanra; Zerit; *Singapore*: Zerit; *Spain*: Zerit; *Swed.*: Zerit; *Switz.*: Zerit; *Thai.*: Stavir; Zerit†; *Turk.*: Zerit; *UK*: Zerit; *USA*: Zerit; *Venez.*: Stavir; Zerit.

Multi-ingredient Preparations. *India*: Emduo-E; Emduo-N; Emduo; Emtri; Lamivir S; Lamostad-N; Lamostad; Triomune; *S. Afr.*: Sonke-LamiNevStav; Triomune; Virtrium; *Thai.*: GPO-Vir S; La-Stavir; *Venez.*: Triomune.

Pharmacopoeial Preparations

USP 36: Stavudine Capsules; Stavudine for Oral Solution.

Telaprevir *(USAN, rINN)*

LY-570310; MP-424; Télaprévir; Telaprevirum; VRT-111950; VX-950; Телапревир.

(1*S*,3a*R*,6a*S*)-2-((2*S*)-2-((2*S*)-Cyclohexyl[(pyrazin-2-ylcarbonyl)amino]acetamido)-3,3-dimethylbutanoyl)-*N*-[(3*S*)-1-cyclopropylamino-1,2-dioxohexan-3-yl]octahydrocyclopenta(*C*)pyrrole-1-carboxamide.

$C_{36}H_{53}N_7O_6$=679.9

CAS — 402957-28-2.

UNII — 65SM5O3W0U.

Uses and Administration

Telaprevir is an oral peptidomimetic HCV-protease inhibitor effective against hepatitis C virus (HCV) serine protease NS3/4A. It is used in the treatment of chronic hepatitis C (p. 952.1) genotype 1 infection in adults with compensated liver disease, including cirrhosis. Telaprevir is given in an oral dose of 750 mg three times daily (once every 7 to 9 hours) with food in a combined regimen with peginterferon alfa and ribavirin (tri-therapy) for 12 weeks. This is followed by 12 or 36 weeks of treatment with peginterferon alfa and ribavirin (bi-therapy) depending on patient history and hepatitis C-RNA (HCV-RNA) levels; UK and US licensed product information gives the following guidance:

For *previously untreated patients* and those who have *relapsed after interferon-based therapy*

- where HCV-RNA is undetectable at weeks 4 and 12: 12 weeks of bi-therapy (total 24 weeks of treatment)
  US licensed product information advises that treatment naive patients with *cirrhosis* may benefit from 36 weeks of bi-therapy (total 48 weeks of treatment); in the UK, this approach is advocated for all patients with cirrhosis irrespective of HCV-RNA levels at weeks 4 and 12
- where HCV-RNA is detectable but 1000 units/mL or less at weeks 4 and/or 12: 36 weeks of bi-therapy (total 48 weeks of treatment)

For *prior partial- and nonresponders to interferon-based therapy*

- 36 weeks of bi-therapy (total 48 weeks of treatment)

For all patients, HCV-RNA levels > 1000 units/mL at week 4 or 12 or detectable HCV-RNA levels at week 24 are an indication of treatment futility, in which case therapy should be abandoned.

The dose of telaprevir may occasionally need to be adjusted to compensate for the effect of an interacting drug. UK-licensed product information for telaprevir recommends a dose of 1.125 g three times daily when telaprevir is to be given with *efavirenz*.

References.

1. Hézode C, *et al.* Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; 360: 1839–50.
2. McHutchison JG, *et al.* Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827–38. Correction. *ibid.*; 361: 1516.
3. McHutchison JG, *et al.* Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; 362: 1292–303. Correction. *ibid.*; 164. [dose]

Adverse Effects

The addition of an HCV-protease inhibitor to a regimen of peginterferon alfa and ribavirin can result in significant additional toxicity, particularly dermatological, gastrointestinal, and haematological. In particular, telaprevir increases the risk of rash, which can include serious skin reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome.

Adverse effects associated with the use of telaprevir with peginterferon alfa and ribavirin are wide ranging, but the most common adverse effects reported in clinical studies were anaemia, rash, itch, nausea, and diarrhoea. Other common effects that have been reported include oral candidiasis, blood dyscrasias (including lymphopenia and thrombocytopenia), hypothyroidism, metabolic disorders (such as hyperuricaemia and hypokalaemia), taste disturbances, syncope, gastrointestinal and anorectal disorders (including anal itch and fissure, haemorrhoids, rectal haemorrhage, and proctalgia), hyperbilirubinaemia, eczema, facial swelling, and peripheral oedema.

Precautions

Telaprevir must not be used as monotherapy as there is a high likelihood of viral resistance developing; because it must always be given with peginterferon alfa and ribavirin, precautions with respect to the use of these medications must be observed (see p. 995.1 and p. 1011.2, respectively).

Telaprevir-containing regimens generally increase the incidence and degree of anaemia compared with peginterferon alfa and ribavirin alone; consequently haemoglobin should be monitored before, and at least every 4 weeks during, telaprevir use. Telaprevir-containing regimens have also been associated with a high incidence of rash, and in rare cases, serious skin reactions such as drug rash with eosinophilia and systemic symptoms and Stevens-Johnson syndrome. If a serious skin reaction occurs, the telaprevir-containing regimen should be permanently and immediately stopped and the patient referred for medical care. Patients who develop mild to moderate rashes should be monitored for progression of rash or development of systemic symptoms, in which case telaprevir should be stopped (although peginterferon alfa and ribavirin may be continued in certain circumstances). Telaprevir is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh class B or C, score ≥7) or in those with decompensated liver disease. Telaprevir may cause modest prolongation of the QT interval, and should be used with caution in patients already at risk for QT-interval prolongation.

Interactions

Telaprevir is an inhibitor of the CYP3A family of cytochrome P450 isoenzymes and is expected to increase exposure to drugs that are metabolised by these enzymes; telaprevir in combination with peginterferon alfa and ribavirin is contra-indicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. Although specific guidance may vary between licensing authorities, these drugs may include:

- the alpha$_1$-adrenoreceptor antagonist alfuzosin
- antiarrhythmics (amiodarone and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- calcium-channel blockers (bepridil)
- ergot derivatives (dihydroergotamine, ergonovine, ergotamine, and methylergonovine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (atorvastatin, lovastatin, and simvastatin)

Owing to the potential for increased serum concentrations of phosphodiesterase type-5 inhibitors (such as sildenafil and tadalafil), telaprevir should be avoided with these drugs when they are given at the doses needed for the treatment of pulmonary hypertension. Similarly, telaprevir may increase serum concentrations of inhaled budesonide, fluticasone, or salmeterol; combination with any of these is not recommended.

Telaprevir is a substrate of the CYP3A group of cytochrome P450 isoenzymes; as a result, drugs that induce or inhibit these enzymes might be expected to decrease or increase exposure to telaprevir. In particular, use with potent inducers of these enzymes (such as carbamazepine, phenobarbital, phenytoin, rifampicin, or St John's wort) should be avoided. Similarly, use with ritonavir-boosted darunavir, fosamprenavir, or lopinavir is not advised; for telaprevir dosing recommendations for co-administration with efavirenz, see Uses and Administration, p. 1016.3. Co-administration with mild or moderate inducers of CYP3A should also be avoided if possible, particularly in patients who are prior nonresponders to peginterferon alfa and ribavirin.

Telaprevir is also an inhibitor and substrate of P-glycoprotein (P-gp). Its use with drugs that are substrates for P-gp transport might be expected to lead to their prolonged therapeutic action or adverse effects; similarly, use with drugs that induce or inhibit P-gp could cause decreased or increased exposure to telaprevir, respectively.

Due to the risk of arrhythmia, telaprevir should not be given with class Ia or III antiarrhythmics (except intravenous lidocaine); it should be used with caution with the class Ic antiarrhythmics propafenone and flecainide. Care is also advised when telaprevir must be used with drugs known to prolong the QT interval.

Hormonal contraception may not be reliable during use of telaprevir, and for up to 2 months after it is stopped. During this time, women of child-bearing potential should use two effective forms of non-hormonal contraception.

Antiviral Action

Telaprevir is an inhibitor of the NS3/4A protease of hepatitis C virus (HCV), a protein involved in the post-translational processing of HCV polyproteins that is required for viral replication. It must always be given with peginterferon alfa and ribavirin to minimise the risk of viral resistance. Although telaprevir was developed to target HCV genotype 1, it also appears to have some activity against genotype 2.

Pharmacokinetics

Telaprevir is absorbed orally, and peak plasma concentrations generally occur about 4 to 5 hours after a dose. Bioavailability is significantly affected by food: compared with a standard meal, telaprevir exposure is increased by 20% when the drug is taken with a high-fat caloric meal, and decreased by 73% when taken on an empty stomach. Telaprevir exposure is also increased by co-administration with peginterferon alfa and ribavirin. It is about 59 to 76% bound to plasma proteins (mainly albumin and alpha 1-acid glycoprotein) and widely distributed to tissues, with a volume of distribution estimated to be in the order of 252 litres (although interindividual variation is about 72%).

Telaprevir is extensively metabolised by the liver via hydrolysis, oxidation, and reduction to produce multiple metabolites; the most prominent are a 30-fold less active *R*-diastereomer of telaprevir (VRT-127394), pyrazinoic acid, and an inactive ketone-reduced metabolite. *In-vitro* studies indicate that CYP3A4 is the main cytochrome P450 isoenzyme responsible for the metabolism of telaprevir, although non-CYP-mediated metabolism likely plays a role as well.

About 90% of a radiolabelled 750-mg dose of telaprevir is recovered within 96 hours of being given, 80% in the faeces (about half of this as unchanged drug or its diastereoisomer), and the remainder in expired air with traces in urine. The steady-state half-life is about 9 to 11 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Incivo; ***Canad.***: Incivek; ***Denm.***: Incivo; ***Fr.***: Incivo; ***Ger.***: Incivo; ***Irl.***: Incivo; ***Israel***: Incivo; ***Jpn***: Telavic; ***Neth.***: Incivo; ***Norw.***: Incivo; ***Spain***: Incivo; ***Swed.***: Incivo; ***Switz.***: Incivo; ***UK***: Incivo; ***USA***: Incivek.

Telbivudine *(BAN, USAN, rINN)*

L-dT; Epavudine; LDT-600; NV-02B; Telbivudina; Telbivudinum; Тельбивудин.

2′-Deoxy-L-thymidine; 1-(2-Deoxy-β-L-*erythro*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione.

$C_{10}H_{14}N_2O_5$=242.2

CAS — 3424-98-4.

ATC — J05AF11.

ATC Vet — QJ05AF11.

UNII — 2OC4HKD3SF.

Uses and Administration

Telbivudine is a L-nucleoside analogue with specific activity against the hepatitis B virus. It is given orally for the treatment of chronic hepatitis B (p. 952.1) in patients with compensated liver disease and evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of telbivudine is 600 mg once daily. For details of dosage modification in patients with renal impairment, see below.

References.

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Administration in renal impairment. Oral doses of telbivudine should be reduced in patients with renal impairment by modifying the dosing interval according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: 600 mg once daily
- CC 30 to 49 mL/minute: 600 mg every 48 hours
- CC less than 30 mL/minute (and not on dialysis): 600 mg every 72 hours
- end stage renal disease: 600 mg every 96 hours

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Adverse Effects

The most common adverse effects reported for telbivudine are cough, dizziness, fatigue, gastrointestinal effects including abdominal pain, diarrhoea, and nausea, and rash. There have also been reports of arthralgia, myalgia, myopathy including myositis, and malaise. Serum amylase, lipase and creatine phosphokinase levels may be increased. Raised serum alanine aminotransferase concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with telbivudine. There have been occasional reports of peripheral neuropathy, particularly when given with peginterferon alfa-2a.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues (see Zidovudine, p. 1024.3).

Precautions

Telbivudine should be given with caution to patients with cirrhosis, hepatomegaly, or other risk factors for liver disease and should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Exacerbation of hepatitis B has been reported both during and after stopping treatment with telbivudine. Liver function should be monitored closely during treatment and for several months after treatment is stopped. Patients taking telbivudine should be monitored for peripheral neuropathy and treatment should be stopped if myopathy or peripheral neuropathy is diagnosed. Dosage reduction may be necessary in patients with renal impairment.

Interactions

Caution should be exercised when telbivudine is given with other drugs that alter renal function; serum concentrations of either drug may be affected. Telbivudine should be given with caution to patients taking other drugs associated with myopathy (such as azole antifungals, ciclosporin, corticosteroids, erythromycin, fibrates, HMG-CoA reductase inhibitors, penicillamine, and zidovudine).

Interferons. For mention of an increased risk of peripheral neuropathy in patients given both telbivudine and *peginterferon alfa-2a*, see Adverse Effects, above.

Antiviral Action

Telbivudine is phosphorylated intracellularly to the active triphosphate form, which competes with thymidine 5′-triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby causing DNA chain termination and inhibiting hepatitis B viral replication.

Telbivudine has no activity against HIV.

Pharmacokinetics

Telbivudine is absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur after about 3 hours. Absorption is not affected when given with food. Binding of telbivudine to plasma proteins is about 3.3% *in vitro*. Telbivudine is not metabolised by the cytochrome P450 system. It is mainly excreted renally by glomerular filtration as unchanged drug, with a terminal elimination half-life of 30 to 53.6 hours. Telbivudine is partially removed by haemodialysis.

References.

1. Zhou XJ, *et al.* Population pharmacokinetics of telbivudine and determination of dose adjustment for patients with renal impairment. *J Clin Pharmacol* 2009; **49**: 725–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sebivo; ***Austral.***: Sebivo; ***Austria***: Sebivo; ***Braz.***: Sebivo; ***Canad.***: Sebivo; ***China***: Sebivo (素比伏); ***Cz.***: Sebivo; ***Denm.***: Sebivo†; ***Fr.***: Sebivo; ***Ger.***: Sebivo; ***Gr.***: Sebivo; ***Hong Kong***: Sebivo; ***Indon.***: Sebivo; ***Irl.***: Sebivo; ***Israel***: Sebivo; ***Ital.***: Sebivo; ***Malaysia***: Sebivo; ***Neth.***: Sebivo; ***Norw.***: Sebivo; ***NZ***: Sebivo; ***Philipp.***: Sebivo; ***Pol.***: Sebivo; ***Port.***: Sebivo; ***Rus.***: Sebivo (Себивo); ***Singapore***: Sebivo†; ***Spain***: Sebivo; ***Swed.***: Sebivo; ***Switz.***: Sebivo; ***Thai.***: Sebivo; ***Turk.***: Sebivo; ***UK***: Sebivo; ***Ukr.***: Sebivo (Себивo); ***USA***: Tyzeka.

Tenofovir *(BAN, USAN, rINN)*

GS-1278; PMPA; (*R*)-PMPA; Tenofovir; Tenofovirum; Tenofovir; Тенофовир.
9-[(*R*)-2-(Phosphonomethoxy)propyl]adenine monohydrate; [[(*R*)-2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl] phosphonic acid monohydrate.
$C_9H_{14}N_5O_4P,H_2O$=305.2
CAS — 147127-20-6 (anhydrous tenofovir); 206184-49-8 (tenofovir monohydrate).
UNII — 99YXE507IL.

Tenofovir Disoproxil Fumarate

(BANM, USAN, rINNM)

Bis(POC)PMPA Fumarate; Fumarato de disoproxilo de tenofovir; GS-4331/05; Ténofovir Disoproxil. Fumarate de; Tenofovir, fumarato del disoproxilo de; Tenofovirum Disoproxilum Fumaras; Тенофовир Дизопроксил Фумарат.
9-[(*R*)-2-[(Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl) methoxy]propyl]adenine fumarate (1:1).
$C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$=635.5
CAS — 202138-50-9.
ATC — J05AF07.
ATC Vet — QJ05AF07.
UNII — OTT9J7900I.

Uses and Administration

Tenofovir is a nucleotide reverse transcriptase inhibitor with antiviral activity against HIV-1 and hepatitis B. It is used in the treatment of HIV infection and AIDS (p. 957.2) and chronic hepatitis B infection (see below). It may also have a role in reducing the transmission of HIV infection (see below). Viral resistance emerges rapidly when tenofovir is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

It is given orally as the disoproxil fumarate ester. Tenofovir disoproxil fumarate 300 mg is equivalent to about 245 mg of tenofovir disoproxil and to about 136 mg of tenofovir. For the treatment of either HIV or chronic **hepatitis B** infection the usual dose is 300 mg of the disoproxil fumarate ester once daily with food. For details of doses in children and adolescents for the treatment of HIV infection, see below.

For details of doses of tenofovir disoproxil fumarate to be used in adult patients with renal impairment, see below.

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing tenofovir disoproxil fumarate in combination with emtricitabine, and with efavirenz plus emtricitabine are available in some countries. It is also a component of a four-drug, fixed-dose combination product with elvitegravir and emtricitabine and the pharmacokinetic enhancer cobicistat (p. 2482.3).

A gel containing tenofovir 1% is under investigation as a topical microbicide in the prevention of HIV infection. For further information see below. A lipid-conjugated formulation, hexadecyloxypropyl tenofovir (CMX-157), thought to have improved antiviral activity due to better intracellular uptake, is also under investigation for the treatment of HIV and AIDS.

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11. Perry CM, Simpson D. Tenofovir disoproxil fumarate: in chronic hepatitis B. *Drugs* 2009; 69: 2245–56.
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Administration in children. For the treatment of **HIV infection** in children from 2 years of age and adolescents, tenofovir disoproxil fumarate is given daily with other antiretroviral drugs. The dose is based on body-weight, which should be monitored periodically and the dose adjusted if necessary.

In the USA, an oral *powder* or *film-coated tablets* are available for use; the film-coated tablets may be given to children weighing 17 kg or more and who are able to swallow intact tablets. The recommended dose for both formulations is 8 mg/kg once daily; doses should not exceed the adult dose (see above).

Administration in renal impairment. Doses of tenofovir disoproxil fumarate should be modified by adjustment of the dosing interval in adult patients with renal impairment according to their creatinine clearance (CC):

- CC 50 mL/minute or more: usual once-daily dosage (see Uses and Administration, above)
- CC 30 to 49 mL/minute: every 48 hours
- CC 10 to 29 mL/minute: every 72 to 96 hours
- haemodialysis patients: a dose every 7 days or after a cumulative total of 12 hours of dialysis

There is a lack of data to make dosage recommendations for children and adolescents with renal impairment.

Hepatitis B. In a meta-analysis evaluating the efficacy of various licensed therapies for chronic hepatitis B in treatment-naive patients,[1] tenofovir was found to be the most effective oral antiviral agent during the first year of treatment in hepatitis B e antigen (HBeAg)-negative patients. In HBeAg-positive patients, tenofovir and entecavir were found to be the most effective treatments.

Much of the data confirming tenofovir's potent effect on hepatitis B viral (HBV) suppression comes from large phase 3 studies involving mainly treatment-naive patients, and whether tenofovir is effective as monotherapy in treatment-experienced patients has been an area of some debate. However, treatment with tenofovir (alone or with emtricitabine) led to complete HBV suppression (at 48 weeks) in 81% of patients who had previously had inadequate response to treatment with adefovir; response was not influenced by the presence of pre-existing antiviral resistance mutations to adefovir or lamivudine.[2] In a similar study in patients who had lamivudine-resistant virus and failed to respond adequately to adefovir therapy, use of tenofovir led to HBV suppression in 46% and 64% of patients at 48 and 96 weeks respectively; the authors noted, however, that efficacy in this heavily pretreated population was inferior to that reported for treatment-naive patients.[3]

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Prevention of HIV transmission. Use of **oral** tenofovir may also have a role in reducing the transmission of HIV infection. In a study involving homosexual men,[1] use of a once-daily, combined oral preparation of tenofovir and emtricitabine led to a 44% lower incidence of HIV infection over and above standard preventative interventions and services (over a median 1.2 years of follow-up). As a result of these data, the CDC has issued guidance[2] on the use of pre-exposure prophylaxis to prevent HIV infection in men who have sex with men. However, one arm of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was reportedly terminated early when interim analysis suggested oral tenofovir was of no value in African women at high risk of infection (FEM-PrEP).[3] Another arm of the study examining oral tenofovir with or without oral emtricitabine in at-risk women was reported to be ongoing.[4] However, more recently[5] it has been reported that 2 studies, whose results remain to be published, have shown that pre-exposure prophylaxis using oral tenofovir with or without emtricitabine is effective.

Tenofovir is being investigated[6-11] as a topical gel for its potential as a microbicide in the prevention of HIV transmission. In a double-blind, placebo-controlled study,[10] use of a tenofovir 1% vaginal gel before and after sexual intercourse reduced the incidence of HIV infection by an estimated 39% overall, and by 54% among women with >80% adherence to the gel regimen. However, contradictory effectiveness outcomes were reported following an interim review of the VOICE study.[11] A 6% rate of HIV infection was reported for both the group receiving the 1% tenofovir vaginal gel and for the placebo group; this arm of the VOICE study was also stopped.

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Adverse Effects

Adverse effects commonly associated with tenofovir either as monotherapy for the treatment of chronic hepatitis B or with other antiretrovirals for the treatment of HIV are mild to moderate gastrointestinal events such as anorexia, abdominal pain and distention, diarrhoea, dyspepsia, flatulence, nausea, and vomiting. Other commonly reported adverse effects are asthenia, dizziness, fatigue, and headache. Rashes may occur. Hypophosphataemia is also common. Serum-amylase concentrations may be raised and pancreatitis has been reported rarely. There have also been reports of raised liver enzymes and hepatitis.

Renal effects, including nephritis, nephrogenic diabetes insipidus, proximal renal tubulopathy (including Fanconi syndrome), and renal failure have been associated with the use of tenofovir, and may occur weeks to months after the start of therapy. Bone pain and osteomalacia, sometimes contributing to fractures, may result from proximal renal tubulopathy; muscle weakness, myopathy, and rarely rhabdomyolysis may also occur.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs; the risk is thought to be low for tenofovir, but cannot be excluded given its structural similarity to the NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including tenofovir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including tenofovir disoproxil fumarate, although tenofovir itself has not been clearly implicated as a causative factor in these effects and has generally been associated with a favourable lipid profile. Tenofovir also appears less likely than the NRTIs to be associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p. 1024.3.

Effects on the kidneys. Use of tenofovir in patients with HIV infection has been associated with renal toxicity,[1] including Fanconi syndrome,[2] interstitial nephritis,[3] and acute renal failure.[4,5] The mechanism of acute renal failure appears to be tubular necrosis, which may not resolve on withdrawal of the drug.[6] Some studies have indicated that glomerular filtration rate or creatinine clearance was consistently decreased in patients given tenofovir-containing regimens;[7,8] it has been reported that this is greater if combined with HIV-protease inhibitors than NNRTIs.[8] Other studies have not found renal toxicity to be a significant problem.[9,10] A systematic review[11] of 17 studies concluded that although use of tenofovir was associated with loss of renal function, the clinical magnitude of the effect was modest; it was concluded that use need not be restricted in areas where facilities for regular monitoring of renal function were not readily available.

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11. Cooper RD, *et al.* Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010; 51: 496–505.

Precautions

Due to the risk of development of HIV resistance, tenofovir must not be used in patients with hepatitis B who are co-infected with HIV, unless it is as part of an appropriate antiretroviral combination regimen. Treatment with tenofovir should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. It should be given with caution to patients with hepatomegaly or other risk factors for liver disease. In particular, extreme caution should be exercised in patients with co-existing hepatitis C infection who are receiving interferon alfa and ribavirin. In patients co-infected with hepatitis B, there is a risk of severe acute exacerbation of hepatitis when tenofovir is stopped, and liver function should be monitored closely in such patients for at least several months.

Renal function and serum phosphate concentrations should be monitored before treatment is started, every 4 weeks during the first year of therapy, and then every 3 months (but see also Effects on the Kidney, p. 1018.3); in patients with a history of renal impairment or who are particularly at risk, more frequent monitoring may be needed; particular risk factors for renal impairment with tenofovir include older age, hypertension, hepatitis C co-infection, lower baseline creatinine clearance, low CD4+ count, and concomitant use of a HIV-protease inhibitor. Tenofovir should be used with caution, and doses modified, in patients with renal impairment. If serum-phosphate concentrations fall markedly or if creatinine clearance is below 50 mL/minute, renal function should be evaluated within a week, and the dose interval may need to be adjusted or treatment interrupted. Tenofovir may be associated with reduction in bone density and patients should be observed for evidence of bone abnormalities; bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia; supplementation with calcium and vitamin D may be beneficial.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tenofovir disoproxil fumarate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Use of tenofovir with nephrotoxic drugs or with other drugs eliminated by active tubular secretion is not recommended; if such use is unavoidable, renal function should be monitored weekly. Tenofovir should not be used with adefovir. Once daily triple drug regimens of tenofovir and lamivudine with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should also be avoided. Tenofovir increases the plasma concentrations of didanosine (see p. 974.1). Decreased plasma concentrations of atazanavir and increased plasma concentrations of tenofovir occur when tenofovir is given with atazanavir; the effect is significantly reduced when ritonavir is added as a booster. Use of ritonavir-boosted lopinavir with tenofovir modestly increases the plasma concentrations of tenofovir.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; 37: 315–16.

Antiviral Action

Tenofovir is converted intracellularly to the diphosphate. This diphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase and incorporation into viral DNA. It also inhibits hepatitis B virus polymerase, resulting in inhibition of viral replication. Tenofovir-resistant strains of HIV have been identified and cross-resistance to other reverse transcriptase inhibitors may occur.

Pharmacokinetics

Tenofovir disoproxil fumarate, a prodrug, is rapidly absorbed and converted to tenofovir after oral doses and peak plasma concentrations occur after 1 to 2 hours. Bioavailability in fasting patients is about 25%, but this is enhanced when tenofovir disoproxil fumarate is taken with a high fat meal. Tenofovir is widely distributed into body tissues, particularly the kidneys and liver. Binding to plasma proteins is less than 1% and that to serum proteins about 7%. The terminal elimination half-life of tenofovir is 12 to 18 hours. Tenofovir is excreted mainly in the urine by both active tubular secretion and glomerular filtration. It is removed by haemodialysis.

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3. Gagnieu MC, *et al.* Population pharmacokinetics of tenofovir in AIDS patients. *J Clin Pharmacol* 2008; 48: 1282–8.
4. Benaboud S, *et al.* Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother* 2011; 55: 1315–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Leuzan; Virakam; Viread; *Austral.*: Viread; *Austria*: Viread; *Belg.*: Viread; *Canad.*: Viread; *Chile*: Viread; *China*: Viread (韦瑞德); *Cz.*: Viread; *Denm.*: Eviplera; Viread; *Fin.*: Viread; *Fr.*: Viread; *Ger.*: Viread; *Gr.*: Viread; *Hong Kong*: Viread; *Hung.*: Viread; *Irl.*: Viread; *Israel*: Viread; *Ital.*: Viread; *Mex.*: Viread; *Neth.*: Viread; *Norw.*: Viread; *NZ*: Viread; *Pol.*: Viread; *Port.*: Viread; *S.Afr.*: Viread; Zefin; *Singapore*: Viread; *Spain*: Viread; *Swed.*: Viread; *Switz.*: Viread; *Thai.*: Ricovir; Viread; *UK*: Viread; *USA*: Viread.

Multi-ingredient Preparations. *Arg.*: Truvada; *Austral.*: Atripla; Truvada; *Austria*: Atripla; Truvada; *Belg.*: Atripla; Truvada; *Canad.*: Atripla; Truvada; *Chile*: Truvada; *Cz.*: Atripla; Truvada; *Denm.*: Atripla; Truvada; *Fin.*: Truvada; *Fr.*: Atripla; Truvada; *Ger.*: Atripla; Eviplera; Truvada; *Gr.*: Atripla; Truvada; *Hong Kong*: Atripla; Truvada; *Irl.*: Atripla; Truvada; *Israel*: Atripla; Eviplera; Truvada; *Ital.*: Atripla; Truvada; *Jpn*: Stribild; *Mex.*: Truvada; *Neth.*: Atripla; Truvada; *Norw.*: Atripla; Eviplera; Truvada; *NZ*: Atripla; Truvada; *Pol.*: Atripla; Truvada; *Port.*: Atripla; Truvada; *S.Afr.*: Adco Emtevir; Didivir; Truvada; Tyricten; *Spain*: Atripla; Truvada; *Swed.*: Atripla; Eviplera; Truvada; *Switz.*: Atripla; Eviplera; Truvada; *Thai.*: Atripla; Ricovir-Em; Truvada; *UK*: Atripla; Eviplera; Stribild; Truvada; *USA*: Atripla; Complera; Stribild; Truvada.

Tilorone Hydrochloride *(USAN, rINNM)*

Hidrocloruro de tilorona; NSC-143969; Tilorone, Chlorhydrate de; Tiloroni Hydrochloridum; Тилорона Гидрохлорид.

2,7-Bis(2-diethylaminoethoxy)fluoren-9-one dihydrochloride.

$C_{32}H_{44}N_2O_3.2HCl$=483.5

CAS — 27591-69-1.

UNII — BJS07J4LKY.

Profile

Tilorone is reported to be an interferon inducer with antiviral and immunomodulatory properties and has been used in the treatment of viral infections; the hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Russ.*: Amixin (Амиксин); Lavomax (Лавомакс); *Ukr.*: Amixin (Амиксин); Lavomax (Лавомакс).

Tipranavir *(rINN)*

PNU-140690; Tipranavirum; Typranawir; U-140690; Типранавир.

3'-[(1*R*)-1-[(6*R*)-5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl]propyl]-5-(trifluoromethyl)-2-pyridinesulfonanilide.

$C_{31}H_{33}F_3N_2O_5S$=602.7

CAS — 174484-41-4.

ATC — J05AE09.

ATC Vet — QJ05AE09.

UNII — ZZT404XD09.

Tipranavir Sodium *(BANM, rINNM)*

Natrii Tipranavirum; PNU-140690E; Tipranavir Disodium (USAN); Tipranavir sodico; Tipranavir Sodique; Натрий Типранавир.

$C_{31}H_{31}F_3N_2Na_2O_5S$=646.6

CAS — 191150-83-1.

ATC — J05AE09.

ATC Vet — QJ05AE09.

UNII — 9BAN2XG1ZW.

Uses and Administration

Tipranavir is a non-peptide HIV-protease inhibitor with antiviral activity against HIV. It is used for the treatment of HIV infection and AIDS (p. 957.2) in treatment-experienced patients or in those with multidrug-resistant HIV infection. Viral resistance emerges rapidly when tipranavir is used alone, and it is therefore used with other antiretrovirals.

It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer (ritonavir-boosted tipranavir). The dose is tipranavir 500 mg (with ritonavir 200 mg) given orally twice daily with food.

For details of doses in children see below.

No dose adjustment is required for patients with renal impairment or mild liver disease. Tipranavir should not be given to patients with moderate to severe liver disease.

Reviews.
1. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. *Drugs* 2005; 65: 1669–77.
2. Doig BJ, Cocohoba JM. Tipranavir: a protease inhibitor for HIV salvage therapy. *Ann Pharmacother* 2006; 40: 1311–21.
3. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. *Clin Pharmacokinet* 2006; 45: 665–82.
4. Temesgen Z, Feinberg J. Tipranavir: a new option for the treatment of drug-resistant HIV infection. *Clin Infect Dis* 2007; 45: 761–9.
5. Orman JS, Perry CM. Tipranavir: a review of its use in the management of HIV infection. *Drugs* 2008; 68: 1435–63.
6. Courter JD, *et al.* Tipranavir: a new protease inhibitor for the pediatric population. *Expert Rev Anti Infect Ther* 2008; 6: 797–803.

Administration in children. For the treatment of HIV infection in children from 2 years of age, tipranavir is given orally with other antiretroviral drugs. It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer. Doses are based on body-weight or body-surface and should not exceed the maximum adult dose (see above).

- The usual recommended dose in children is: tipranavir 14 mg/kg (with ritonavir 6 mg/kg) twice daily *or* tipranavir 375 mg/m^2 (with ritonavir 150 mg/m^2) twice daily
- US licensed product information suggests that children who are intolerant or develop toxicities to the usual dose may take a reduced dose, provided that their virus is not resistant to multiple HIV-protease inhibitors: tipranavir 12 mg/kg (with ritonavir 5 mg/kg) twice daily *or* tipranavir 290 mg/m^2 (with ritonavir 115 mg/m^2) twice daily

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing tipranavir are gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, and vomiting), fatigue, and headache. Serious adverse effects reported include increased risk of bleeding and intracranial haemorrhage including some fatalities. Severe hepatotoxicity (hepatitis and hepatic decompensation, including some fatalities) has also occurred; ritonavir-boosted tipranavir appears to be more likely to cause adverse hepatic events than other HIV-protease inhibitors. Rashes, generally occurring after about 2 months of treatment and lasting about 3 weeks have been reported; rashes are sometimes accompanied by joint pain, stiffness, throat tightness, or generalised pruritus.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including tipranavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement

(buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including tipranavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p. 986.2.

Intracranial haemorrhage. In June 2006, the manufacturer (*Boehringer Ingelheim, USA*) reported that there had been 14 reports of intracranial haemorrhage (ICH) linked to the use of ritonavir-boosted tipranavir, including 8 fatalities, among about 7000 HIV-1 infected patients in clinical trials.[1] The median time to onset of an ICH event was 525 days. It was noted that many of these patients had other risk factors for ICH, such as CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or use of anticoagulants or antiplatelet drugs. The FDA and EMEA subsequently advised that ritonavir-boosted tipranavir should be used with caution in patients at risk of bleeding; it should be noted that routine monitoring of coagulation parameters is not indicated as no pattern of abnormal coagulation parameters has been seen in patients taking tipranavir, or before the development of tipranavir-associated ICH. However, a cohort study[2] estimating the background rate of ICH, and comparing it to that in tipranavir users estimated that 455 to 5000 HIV-infected patients would need to be given tipranavir for 1 year to cause 1 extra case of ICH over the background rate.

There has also been a report of ICH in a patient using tipranavir whose only apparent predisposing factor was cryptococcal meningitis.[3]

1. Boehringer Ingelheim, USA. Important safety information: intracranial hemorrhage in patients receiving Aptivus (tipranavir) capsules (issued 30th June 2006). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153070.pdf (accessed 16/03/11)
2. Justice AC, *et al.* Drug toxicity, HIV progression, or comorbidity of aging: does tipranavir use increase the risk of intracranial hemorrhage? *Clin Infect Dis* 2008; 47: 1226–30.
3. Chrysos G, *et al.* Intracranial haemorrhage possibly related to tipranavir in an HIV-1 patient with cryptococcal meningitis. *J Infect* 2008; 57: 85–7.

Precautions

Tipranavir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh class B or C), and should be used with caution in those with mild impairment (Child-Pugh A). Treatment should not be started in patients with pretreatment liver enzyme values more than 5 times the upper limit of normal. Patients should be closely monitored for clinical signs and symptoms of hepatitis; monitoring of liver enzymes is recommended before and during treatment with tipranavir. In patients with mild hepatic impairment, chronic hepatitis, or other underlying liver disease more frequent monitoring is recommended. Treatment should be interrupted or stopped if liver function deteriorates and should be permanently stopped if liver enzyme values increase to more than 10 times the upper limit of normal or if signs or symptoms of clinical hepatitis develop. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients who are at increased risk of bleeding, due to trauma, surgery, or certain medical conditions (such as haemophilia A or B) or who are taking antiplatelet drugs or anticoagulants, as reports of spontaneous bleeding and intracranial haemorrhage have been associated with the use of tipranavir. Tipranavir oral solution contains vitamin E and patients given the oral solution should not take high doses of supplemental vitamin E.

Tipranavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy.

Interactions

Tipranavir is both an inducer and an inhibitor of the cytochrome P450 isoenzyme CYP3A4 although when given with low-dose ritonavir there is a net inhibition of CYP3A4; there is therefore the potential for complex interactions with other drugs metabolised by this enzyme. Ritonavir-boosted tipranavir is also a net inducer of P-glycoprotein.

Although specific guidance varies between licensing authorities, licensed product information generally contra-indicates the use of ritonavir-boosted tipranavir with drugs that are highly dependent on CYP3A4 or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. In the UK, these drugs include

- antiarrhythmics (amiodarone, bepridil, flecainide, metoprolol in doses used for heart failure, propafenone, and quinidine)
- antihistamines (astemizole and terfenadine)
- antipsychotics (pimozide)
- ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine)
- gastrointestinal prokinetics (cisapride)
- sedatives and hypnotics (triazolam and oral midazolam)
- statins (simvastatin and lovastatin)

Use with halofantrine, lumefantrine, or tolterodine is also not recommended. In the USA, use with the alpha$_1$-adrenoceptor antagonist alfuzosin is also contra-indicated. Owing to the potential for increased serum concentrations of sildenafil, ritonavir-boosted tipranavir should be avoided with sildenafil when given at the doses needed for the treatment of pulmonary hypertension. Similarly, ritonavir-boosted tipranavir may increase serum concentrations of inhaled fluticasone and salmeterol and combination is not recommended. Rifampicin and St John's wort decrease the concentration of tipranavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p. 987.2.

Antiviral Action

Tipranavir is a non-peptide HIV-protease inhibitor. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. HIV isolates resistant to tipranavir have been reported and viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Tipranavir is absorbed to a limited extent after oral doses. Food improves the tolerability and bioavailability is increased with a high fat meal. Peak plasma concentrations occur within 1 to 5 hours and steady state is usually reached after 7 to 10 days of treatment. Tipranavir is about 99.9% bound to plasma proteins. It is metabolised by the cytochrome P450 system (mainly the isoenzyme CYP3A4), although when given with ritonavir metabolism is minimal with the majority of tipranavir being excreted unchanged in the faeces. The mean elimination half-life of tipranavir is 4.8 to 6 hours.

References.

1. Weizsaecker K, *et al.* Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. *Int J STD AIDS* 2011; 22: 294–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aptivus; *Austral.*: Aptivus; *Austria*: Aptivus; *Belg.*: Aptivus; *Braz.*: Elodius; *Canad.*: Aptivus; *Cz.*: Aptivus; *Denm.*: Aptivus; *Fin.*: Aptivus†; *Fr.*: Aptivus; *Ger.*: Aptivus; *Gr.*: Aptivus; *Hung.*: Aptivus; *Irl.*: Aptivus; *Ital.*: Aptivus; *Mex.*: Aptivus; *Neth.*: Aptivus; *Norw.*: Aptivus†; *Pol.*: Aptivus; *Port.*: Aptivus; *Spain*: Aptivus; *Swed.*: Aptivus; *Switz.*: Aptivus; *UK*: Aptivus; *USA*: Aptivus.

Trichosanthin

Compound Q; GLQ-223 (a purified form of trichosanthin); Tricosantina.

CAS — 60318-52-7 (trichosanthins); 116899-30-0 (Trichosanthes kirilowii); 160185-58-0 (Trichosanthes kirilowii root); 120947-28-6 (GLQ-223).

Profile

Trichosanthin is a polypeptide extracted from the tuber of the Chinese cucumber, *Trichosanthes kirilowii* (Cucurbitaceae). It has been investigated in the treatment of HIV infection and is used in China as an abortifacient.

HIV infection and AIDS. Trichosanthin has been given to patients with AIDS, AIDS-related complex, or HIV infection.[1,2] It has generally been given by intravenous injection, the use of the intramuscular route having been abandoned due to the occurrence of pain and necrosis at the injection site.[1] A common adverse effect with intravenous use was a flu-like syndrome with headache, myalgias, fever, and arthralgia and was generally mild to moderate,[3] although neurological effects progressing to coma with fatalities have been reported.[1,2] Improvements in surrogate markers for HIV infection have been reported including increases in CD4+ T lymphocyte counts in patients with moderate disease[3] and in patients failing to respond to reverse transcriptase inhibitors.[4]

1. Byers VS, *et al.* A phase I/II study of trichosanthin treatment of HIV disease. *AIDS* 1990; 4: 1189–96.
2. Kahn JO, *et al.* The safety and pharmacokinetics of GLQ223 in subjects with AIDS and AIDS-related complex: a phase I study. *AIDS* 1990; 4: 1197–1204.
3. Kahn JO, *et al.* Safety, activity, and pharmacokinetics of GLQ223 in patients with AIDS and AIDS-related complex. *Antimicrob Agents Chemother* 1994; 38: 260–7.
4. Byers VS, *et al.* A phase II study of effect of addition of trichosanthin to zidovudine in patients with HIV disease and failing antiretroviral agents. *AIDS Res Hum Retroviruses* 1994; 10: 413–20.

Trifluridine *(USAN, rINN)*

F_3T; F_3TDR; NSC-75520; Trifluorothymidine; Trifluorothymidinum; Trifluorotymidlini; Trifluorotymidin; Trifluridiini; Trifluridin; Trifluridina; Trifluridinum; Трифлуридин.

αα-Trifluorothymidine; 2′-Deoxy-5-trifluoromethyluridine.

$C_{10}H_{11}F_3N_2O_5$=296.2

CAS — 70-00-8.

ATC — S01AD02.

ATC Vet — QS01AD02.

UNII — RMW9VSRW38.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Trifluridine). A white, crystalline powder. Soluble in water. Protect from light.

USP 36: (Trifluridine). A white, odourless powder appearing under the microscope as rod-like crystals. Store in airtight containers. Protect from light.

Uses and Administration

Trifluridine is a pyrimidine nucleoside structurally related to thymidine. It is used in the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex viruses (p. 955.2). One drop of a 1% ophthalmic solution is instilled into the eye every 2 hours up to a maximum of 9 times daily until complete re-epithelialisation has occurred. Treatment is then reduced to one drop every 4 hours to a minimum of 5 drops daily for a further 7 days. Treatment should not be continued for more than a total of 21 days.

Trifluridine, alone or as a combined formulation with a thymidine phosphorylase inhibitor to reduce its metabolism (TAS-102), has been investigated in the treatment of malignant neoplasms.

Reviews.

1. Heidelberger C, King DH. Trifluorothymidine. *Pharmacol Ther* 1979; 6: 427–42.
2. Carmine AA, *et al.* Trifluridine: a review of its antiviral activity and therapeutic use in the topical treatment of viral eye infections. *Drugs* 1982; 23: 329–53.
3. Temmink OH, *et al.* Therapeutic potential of the dual-targeted TAS-102 formulation in the treatment of gastrointestinal malignancies. *Cancer Sci* 2007; 98: 779–89.
4. Wilhelmus KR. Antiviral treatment and other therapeutic intervention for herpes simplex virus epithelial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2011 (accessed 15/03/11).

Adverse Effects

Adverse effects occurring after the use of trifluridine in the eyes are similar to those for idoxuridine (p. 985.1) but have been reported to occur less frequently.

References.

1. Udell IJ. Trifluridine-associated conjunctival cicatrization. *Am J Ophthalmol* 1985; 99: 363–4.

Antiviral Action

Trifluridine acts similarly to idoxuridine to interfere with viral DNA synthesis after phosphorylation. It is reported to be active against herpes simplex viruses, some adenoviruses, vaccinia viruses, and CMV. Like idoxuridine it is incorporated into mammalian DNA.

Pharmacokinetics

Trifluridine is absorbed through the cornea after application to the eye and penetration may be increased in the presence of damage or inflammation. Systemic absorption does not appear to follow ocular administration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Viroptic; *Fr.*: Virophta; *Ger.*: Triflumann; *Gr.*: Thilol; Triherpine; Viromidin; *Ital.*: Triherpine†; *Neth.*: TFI Ophtiole†; *Port.*: Viridin†; *S.Afr.*: TFI; *Thai.*: Triherpine†; *Turk.*: TFT-Thilo; *USA*: Viroptic.

Pharmacopoeial Preparations

BP 2014: Trifluridine Eye Drops.

Tromantadine Hydrochloride *(rINNM)*

D-41; Hidrocloruro de tromantadina; Tromantadina, hidrocloruro de; Tromantadine, Chlorhydrate de; Tromantadinhydrochlorid; Tromantadini Hydrochloridum; Тромантадина Гидрохлорид.

N-1-Adamantyl-2-(2-dimethylaminoethoxy)acetamide hydrochloride; 2-(2-Dimethylaminoethoxy)-*N*-(tricyclo [3.3.1.1^{3,7}]dec-1-yl)acetamide hydrochloride.

$C_{16}H_{28}N_2O_2$,HCl=316.9

CAS — 53783-83-8 (tromantadine); 41544-24-5 (tromantadine hydrochloride).

ATC — D06BB02; J05AC03.

ATC Vet — QD06BB02; QJ05AC03.

UNII — H09LUS437B.

Profile

Tromantadine hydrochloride is a derivative of amantadine (p. 890.3) used for its antiviral activity. It is applied topically at a concentration of 1% in the treatment of herpes simplex infections of the skin and mucous membranes (p. 955.2).

Contact dermatitis has been reported after the topical use of tromantadine hydrochloride.

Effects on the skin. References to contact dermatitis associated with the use of tromantadine.

1. Panta D, Mischer P. Contact dermatitis from tromantadine hydrochloride. *Contact Dermatitis* 1976; **2**: 282–4.
2. Lembo G, *et al.* Allergic dermatitis from Viruserol ointment probably due to tromantadine hydrochloride. *Contact Dermatitis* 1984; **10**: 317.
3. Jauregui I, *et al.* Allergic contact dermatitis from tromantadine. *J investig Allergol Clin Immunol* 1997; **7**: 260–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Viru-Merz Serol; ***Braz.***: Herpex; ***Cz.***: Viru-Merz; ***Ger.***: Viru-Merz Serol; ***Gr.***: Viru-Merz Serol; ***Hong Kong***: Viru-Merz; ***Hung.***: Viru-Merz; ***Indon.***: Viru-Merz; ***Israel***: Viru-Merz; ***Ital.***: Drolanin; ***Malaysia***: Viru-Merz; ***Mex.***: Viru-Serol; ***Philipp.***: Viru-Merz†; ***Pol.***: Viru-Merz; ***Port.***: Viru-Merz; ***Rus.***: Viru-Merz Serol (Виру-Мерц Серол); ***Singapore***: Viru-Merz; ***Spain***: Viru-Serol†; ***Switz.***: Viru-Merz Serol†.

Valaciclovir Hydrochloride

(BANM, rINNM)

256U87 (valaciclovir); Hidrocloruro de valaciclovir; Valaciclovir, Chlorhydrate de; Valaciclovir, hidrocloruro de; Valaciclovir hydrochloridum; Valacyclovir Hydrochloride (USAN); Валацикловира Гидрохлорид.

L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine hydrochloride.

$C_{13}H_{20}N_6O_4$,HCl=360.8

CAS — 124832-26-4 (valaciclovir); 124832-27-5 (valaciclovir hydrochloride).

ATC — J05AB11.

ATC Vet — QJ05AB11.

UNII — G447S0T1VC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Valaciclovir Hydrochloride, Anhydrous). A white or almost white powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in anhydrous alcohol.

USP 36: (Valacyclovir Hydrochloride). A white to off-white powder. Soluble in water; insoluble in dichloromethane. Store in airtight containers at a temperature below 30 degrees.

Uses and Administration

Valaciclovir is a prodrug of the antiviral aciclovir (p. 964.1). It is used in the treatment of herpes zoster (p. 956.2) and herpes simplex infections (p. 955.2) of the skin and mucous membranes, including genital herpes. Treatment should be started as soon as symptoms occur; ideally within 48 to 72 hours. In immunocompromised patients treatment for herpes zoster may be given to patients who present within one week of vesicle formation or at any time before full crusting of lesions. Valaciclovir is also used for the suppression of recurrent herpes simplex infections and can reduce the risk of transmission of genital herpes to susceptible partners when used as suppressive therapy and as part of safer sex practices. It is also used for the prophylaxis of CMV infection after solid organ transplantation.

Valaciclovir is given orally as the hydrochloride; doses are expressed in terms of the base. Valaciclovir hydrochloride 1.11 g is equivalent to about 1 g of valaciclovir.

For herpes zoster, the dose is 1 g three times daily for 7 days in immunocompetent patients; in immunocompromised patients treatment should be continued for a further 2 days after crusting of lesions.

For treatment of **herpes simplex infections** in immunocompetent patients, 500 mg is given twice daily for 3 to 5 days for recurrent episodes or for up to 10 days for a first episode; in the USA, the recommended dose for a first episode of genital herpes is 1 g twice daily for 10 days. For treatment of herpes simplex infections in immunocompromised patients the recommended dose is 1 g twice daily for at least 5 days for recurrent episodes or for up to 10 days for initial episodes.

For the *suppression* of herpes simplex infection in immunocompetent patients, a dose of 500 mg daily (as a single dose, or in two divided doses in those with very frequent recurrences), is recommended; in the USA, a dose of 1 g once daily is recommended for suppression of recurrent genital herpes, although for those with a history of 9 or fewer recurrences per year, a dose of 500 mg once daily is also considered sufficient. A dose of 500 mg twice daily may be used in immunocompromised patients. To *reduce transmission* of genital herpes in those with a history of 9 or fewer recurrences per year a dose of 500 mg once daily is taken by the infected partner.

For the treatment of herpes labialis, a total daily dose of 4 g given in two divided doses 12 hours apart (but not less than 6 hours apart) is suggested as an alternative regimen for immunocompetent persons.

A dose of 2 g four times daily is recommended for prophylaxis of **CMV infection** in solid organ transplant recipients; prophylaxis should begin as soon as possible post-transplant and is usually continued for 90 days.

For doses used in children or in patients with renal impairment, see below.

References.

1. Ormrod D, *et al.* Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000; **59**: 839–63.
2. Ormrod D, Goa K. Valaciclovir: a review of its use in the management of herpes zoster. *Drugs* 2000; **59**: 1317–40.
3. Tyring SK, *et al.* Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. *J Infect Dis* 2002; **186** (suppl 1): S40–S46.
4. Corey L, *et al.* Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350**: 11–20.
5. Brantley JS, *et al.* Valacyclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006; **4**: 367–76.
6. Fife KH, *et al.* Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81**: 1321–7.
7. Vigil KJ, Chemaly RF. Valacyclovir: approved and off-label uses for the treatment of herpes virus infections in immunocompetent and immunocompromised adults. *Expert Opin Pharmacother* 2010; **11**: 1901–13.

Administration in children. Although not licensed for this use in the UK, in the USA valaciclovir is indicated for the treatment of chickenpox (varicella) in immunocompetent children from 2 up to 18 years of age. An oral dose of 20 mg/kg (to a maximum of 1 g) 3 times daily for 5 days is recommended; treatment should begin within 24 hours of the onset of rash. Valaciclovir is available in the USA as a solid oral dosage form (*Valtrex Caplets; GSK, USA*). Licensed product information includes specifications for extemporaneous preparation of an oral suspension containing 25 or 50 mg/mL to facilitate appropriate dosing in children, by grinding the caplets and suspending in Suspension Structured Vehicle *USNF* with a suitable flavouring agent. The resultant suspension is stored at 2 to 8 degrees and used within 28 days of preparation.

In the UK, valaciclovir is licensed for use in the prophylaxis of CMV infection after renal transplantation in children from 12 years of age; doses are the same as those in adults (above). The *BNFC* considers that valaciclovir may also be given, if necessary, to children 12 years and over for herpes zoster (in immunocompromised children) and treatment and suppression of herpes simplex, in doses equivalent to those in adults.

Administration in renal impairment. Oral doses of valaciclovir may need to be reduced in patients with renal impairment. The following adjusted doses are suggested according to creatinine clearance (CC):

Immunocompetent patients:

Herpes zoster.

- CC 30 to 49 mL/minute: 1 g every 12 hours
- CC 10 to 29 mL/minute: 1 g every 24 hours
- CC less than 10 mL/minute: 500 mg every 24 hours

Acute episodes of herpes simplex infection (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 500 mg every 12 hours
- CC less than 30 mL/minute: 500 mg every 24 hours

US licensed product information recommends:

- CC 10 to 29 mL/minute: 1 g every 24 hours for initial episodes of genital herpes; 500 mg every 24 hours for recurrence
- CC less than 10 mL/minute: 500 mg every 24 hours for both initial and recurrent episodes of genital herpes

Suppression of recurrent herpes simplex (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 500 mg every 24 hours; those with 10 or more relapses a year: 250 mg every 12 hours
- CC less than 30 mL/minute: 250 mg every 24 hours

US licensed product information recommends:

- CC less than 30 mL/minute: 500 mg every 24 hours; those with 9 or fewer relapses a year: 500 mg every 48 hours

Reduction of transmission of genital herpes.

- CC less than 15 mL/minute: 250 mg every 24 hours

Alternative regimen for herpes labialis.

- CC 30 to 49 mL/minute: 1 g every 12 hours for 2 doses
- CC 10 to 29 mL/minute: 500 mg every 12 hours for 2 doses
- CC less than 10 mL/minute: 500 mg as a single dose

Immunocompromised patients:

Herpes zoster

- CC 30 to 49 mL/minute: 1 g every 12 hours
- CC 10 to 29 mL/minute: 1 g every 24 hours
- CC less than 10 mL/minute: 500 mg every 24 hours

Acute episodes of herpes simplex infection (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 1 g every 12 hours
- CC less than 30 mL/minute: 1 g every 24 hours

Suppression of recurrent herpes simplex (including genital herpes).

UK licensed product information recommends:

- CC 30 mL/minute or more: 500 mg every 12 hours
- CC less than 30 mL/minute: 500 mg every 24 hours

US licensed product information recommends:

- CC less than 30 mL/minute: 500 mg every 24 hours

Prophylaxis of CMV.

- CC 50 to 74 mL/minute: 1.5 g every 6 hours
- CC 25 to 49 mL/minute: 1.5 g every 8 hours
- CC 10 to 24 mL/minute: 1.5 g every 12 hours
- CC less than 10 mL/minute: 1.5 g every 24 hours

Patients requiring haemodialysis should receive the lowest recommended dose after the dialysis run. Supplementary doses are not needed after chronic ambulatory peritoneal dialysis or continuous arteriovenous haemofiltration/dialysis.

HIV infection. For information on the use of valaciclovir in the treatment of patients co-infected with herpes simplex virus type 2 and HIV-1 see under Aciclovir, p. 964.3.

Sickle-cell disease. A preliminary study[1] of the use of valaciclovir as an antisickling agent in the management of sickle-cell disease (p. 1123.2).

1. Ender KL, *et al.* Safety of short-term valacyclovir as an anti-sickling agent in sickle-cell anemia. *Pediatr Blood Cancer* 2011; **56**: 843–5.

Adverse Effects and Precautions

As for Aciclovir, p. 965.1.

Breast feeding. In a study in 5 women who took oral valaciclovir 500 mg twice daily for 7 days, concentrations of the active metabolite aciclovir in breast milk were 3.4 times those in maternal serum at 4 hours after the initial dose, although the ratio declined to 1.85 at steady-state concentrations. Nonetheless, it was calculated that the amount ingested by an infant would be negligible (about 2% of a standard neonatal dose of intravenous aciclovir, with exposure further reduced by the poor oral bioavailability of the drug), and valaciclovir was thus considered compatible with breast feeding.[1]

1. Sheffield JS, *et al.* Acyclovir concentrations in human breast milk after valaciclovir administration. *Am J Obstet Gynecol* 2002; **186**: 100–102.

Effects on the nervous system. Mononeuritis multiplex due to vasculitis has been reported[1] in a woman a week after a one-day course of valaciclovir for the treatment of herpes labialis. Symptoms improved within 10 days of treatment with oral prednisolone but reoccurred upon rechallenge with valaciclovir.

1. Pary LF, *et al.* Vasculitic mononeuritis multiplex induced by valacyclovir. *Neurology* 2004; **62**: 1906–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valaciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Pregnancy. For information on the use of valaciclovir in pregnancy see under Precautions of Aciclovir, p. 965.3.

Interactions

As for Aciclovir, p. 966.1.

Antiviral Action

As for Aciclovir, p. 966.1.

Pharmacokinetics

As for Aciclovir, p. 966.2.

Valaciclovir is readily absorbed from the gastrointestinal tract after oral doses, and is rapidly and almost completely converted to aciclovir and valine by first-pass intestinal or hepatic metabolism. After a 1-g oral dose of valaciclovir, bioavailability of aciclovir is about 54% with peak plasma concentrations occurring after 1 to 2 hours. Valaciclovir is eliminated mainly as aciclovir and its metabolite 9-carboxymethoxymethylguanine; less than 1% of a dose of valaciclovir is excreted unchanged in the urine.

References.

1. Steingrimsdottir H, *et al.* Bioavailability of aciclovir after oral administration of aciclovir and its prodrug valaciclovir to patients with leukopenia after chemotherapy. *Antimicrob Agents Chemother* 2000; 44: 207–9.
2. Höglund M, *et al.* Comparable aciclovir exposures produced by oral valaciclovir and intravenous aciclovir in immunocompromised cancer patients. *J Antimicrob Chemother* 2001; 47: 855–61.
3. Bras AP, *et al.* Comparative bioavailability of acyclovir from oral valacyclovir and acyclovir in patients treated for recurrent genital herpes simplex virus infection. *Can J Clin Pharmacol* 2001; 8: 207–11.
4. Nadal D, *et al.* An investigation of the steady-state pharmacokinetics of oral valacyclovir in immunocompromised children. *J Infect Dis* 2002; 186 (suppl 1): S123–S130.
5. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. *J Antimicrob Chemother* 2004; 53: 899–901.
6. Kimberlin DW, *et al.* Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. *Clin Infect Dis* 2010; 50: 221–8.
7. Smith JP, *et al.* Pharmacokinetics of acyclovir and its metabolites in cerebrospinal fluid and systemic circulation after administration of high-dose valacyclovir in subjects with normal and impaired renal function. *Antimicrob Agents Chemother* 2010; 54: 1146–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Valtrex; Viramixal; Viranet; *Austral.*: Vaclovir; Valacor; Valnir; Valnir; Valtrex; Valvala; Zelitrex; *Austria*: Valtrex; Viropel; *Belg.*: Zelitrex; *Braz.*: Valtrex; *Canad.*: Valtrex; *Chile*: Pervioral; Vacper; Vadiral; Valtrex; *China*: A Mai Xin (阿迈新); Kenong (科依); Li Ke Fen (丽科分); Lizhuwei (丽珠威); Ming Zhu Xin (明竹欣); Valtrex (维德思); *Cz.*: Valtrex; *Denm.*: Zelitrex; *Fin.*: Valavir; Valtrex; *Fr.*: Zelitrex; *Ger.*: Valtrex; *Gr.*: Valtrex; Vociflon; *Hong Kong*: Valtrex; *India*: Valcivir; *Indon.*: Herclov; Inclovir; Valtrex; Valvir; *Irl.*: Myval; Valotix; Valtrex; *Israel*: Valtrex; *Ital.*: Talavir; Zelitrex; *Malaysia*: Valtrex; *Mex.*: Rapivir; Valinir; *Neth.*: Zelitrex; *Norw.*: Valtrex; *NZ*: Valtrex; *Philipp.*: Valtrex; *Pol.*: Valtrex; *Port.*: Crotax; Sades; Ticofarma; Valavir; Valtrex; *Rus.*: Vacirex (Вацирекс); Valtrex (Валтрекс); *S.Afr.*: Anviro; Zelitrex; Zelivire; *Singapore*: Valtrex; *Spain*: Tridiavir; Valherpes†; Valtrex; Virval†; *Swed.*: Valtrex; *Switz.*: Valtrex; *Thai.*: Valtrex; *Turk.*: Valtrex; *UK*: Valtrex; *Ukr.*: Gerpeval (Герпевал); Valavir (Валавир); Valmax (Вальмакс); Valtrex (Вальтрекс); Valtrovir (Вальтровир); *USA*: Valtrex; *Venez.*: Valtrex.

Pharmacopoeial Preparations

USP 36: Valacyclovir Oral Suspension; Valacyclovir Tablets.

Valganciclovir Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de valganciclovir; Ro-107-9070/194; RS-079070-194; Valganciclovir, Chlorhydrate de; Valganciclovir, hidrocloruro de; Valganciclóviri Hydrochloridum; Валганцикловира Гидрохлорид

L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy] methyl]-guanine hydrochloride

$C_{14}H_{22}N_6O_5$,HCl=390.8

CAS — 175865-60-8 (valganciclovir); 175865-59-5 (valganciclovir hydrochloride)

ATC — J05AB14

ATC Vet — QJ05AB14

UNII — 4P3T9QF9NZ

Pharmacopoeias. In *US.*

USP 36: (Valganciclovir Hydrochloride). A white to off-white powder. Very slightly soluble in alcohol; practically insoluble in isopropyl alcohol, in acetone, in hexane, and in ethyl acetate. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability.

References.

1. Analizi NE, *et al.* Stability of valganciclovir in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; 59: 1267–70.
2. Henkin CC, *et al.* Stability of valganciclovir in extemporaneously compounded liquid formulations. *Am J Health-Syst Pharm* 2003; 60: 687–90.

Uses and Administration

Valganciclovir is a prodrug of the antiviral ganciclovir (p. 982.3) that is used for the treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in transplant recipients who have received an organ from a CMV-positive donor (see below).

Valganciclovir is given orally with food as the hydrochloride; doses are expressed in terms of the base. Valganciclovir hydrochloride 1.1 g is equivalent to about 1 g of valganciclovir.

For *induction* in patients with active **CMV retinitis**, the dose is 900 mg twice daily for 21 days. For *maintenance* after induction, or in patients with inactive CMV retinitis, the dose is 900 mg once daily. Patients whose retinitis deteriorates during maintenance may repeat induction but the possibility of viral resistance should be considered. For *prevention* of CMV disease in **organ transplant** recipients, the dose is 900 mg daily starting within 10 days and continuing until 100 days after transplantation. Prophylaxis for kidney transplant patients may be given daily for 200 days after transplantation, but the possible risk of developing leucopenia and neutropenia should be considered.

For valganciclovir doses used in children or patients with renal impairment, see below.

Reviews.

1. Freeman RB. Valganciclovir: oral prevention and treatment of cytomegalovirus in the immunocompromised host. *Expert Opin Pharmacother* 2004; 5: 2007–16.
2. Cvetković RS, Wellington K. Valganciclovir: a review of its use in the management of CMV infection and disease in immunocompromised patients. *Drugs* 2005; 65: 859–78.
3. Pescovitz MD. Valganciclovir: recent progress. *Am J Transplant* 2010; 10: 1359–64.
4. Asberg A, *et al.* Valganciclovir for the prevention and treatment of CMV in solid organ transplant recipients. *Expert Opin Pharmacother* 2010; 11: 1159–66.

Administration in children. Although not recommended in the UK for patients younger than 18 years, in the USA valganciclovir is licensed for use in the prevention of CMV disease in children aged 4 months to 16 years who have received a heart or kidney transplant. The oral solution is the preferred formulation for children since it allows for more accurate dosing; however, tablets can be used if the dose required is a multiple of 450 mg (the available strength) or within 10% of this. The recommended oral daily dose is calculated with a formula based on body-surface and creatinine clearance (to a maximum of 900 mg) and rounded to the nearest 25-mg increment. Licensed product information (*Valcyte; Roche, USA*)[1] should be consulted for details of the formula. Dosing should begin within 10 days of transplantation, and be continued until 100 days post-transplantation.

1. Roche USA. Valcyte Full Prescribing Information (issued August 2010). Available at: http://www.gene.com/gene/products/information/valcyte/pdf/pi.pdf (accessed 15/10/10)

Administration in renal impairment. Doses of oral valganciclovir should be reduced in renal impairment according to creatinine clearance (CC). Licensed product information recommends the following doses:

- CC 40 to 59 mL/minute: 450 mg twice daily for *induction* and 450 mg once daily for *maintenance* or *prevention*
- CC 25 to 39 mL/minute: 450 mg once daily for *induction* and 450 mg every two days (or 225 mg once daily) for *maintenance* or *prevention*
- CC 10 to 24 mL/minute: 450 mg every two days (or 225 mg once daily) for *induction* and 450 mg twice weekly (or 125 mg once daily) for *maintenance* or *prevention*
- haemodialysis patients: 200 mg 3 times a week for *induction* and 100 mg 3 times a week for *maintenance* or *prevention*; doses should be given after the dialysis session

Cytomegalovirus infections. Valganciclovir produces high systemic concentrations of ganciclovir after oral doses; exposure may be higher than with intravenous ganciclovir regimens.[1] It is therefore active against CMV infections (p. 954.2). It has been shown to be of benefit for both induction therapy and maintenance treatment of CMV retinitis in patients with AIDS,[2–4] and although this has become less widespread in the developed world with the advent of HAART, it continues to be a problem in resource-poor settings in particular; there have been calls for valganciclovir to be made more widely available for treatment in preference to less effective and convenient drugs.[3]

Valganciclovir is also used in the prophylaxis and preemptive treatment of CMV infections in transplant recipients,[5–10] and many centres consider it to be the standard of care for this indication (including in liver transplantation although it is not licensed for such use in the USA—see Adverse Effects, Treatment, and Precautions, below).[11] Late-onset disease (occurring after the drug is stopped) may be a problem with prophylactic regimens (particularly in CMV-negative patients given a CMV-positive graft) and extended prophylactic regimens after kidney[12,13] and lung[14] transplantation have therefore been investigated;[12,14] for kidney transplant patients licensed product information indicates that prophylaxis may be continued until 200 days after transplantation. The problem of late-onset disease is negligible with pre-emptive treatment.[15]

1. Einsele H, *et al.* Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood* 2006; 107: 3002–8.
2. Martin DF, *et al.* Valganciclovir Study Group. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med* 2002; 346: 1119–26. Correction. *ibid.*; 347: 862.
3. Heiden D, *et al.* Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. *PLoS Med* 2007; 4: e334. Available at: http://medicine.plosjournals.org/archive/1549-1676/4/12/pdf/10.1371_journal.pmed.0040334-S.pdf (accessed 28/08/08)
4. Patil AJ, *et al.* Valganciclovir in the treatment of cytomegalovirus retinitis in HIV-infected patients. *Clin Ophthalmol* 2010; 4: 111–19.
5. Paya C, *et al.* Valganciclovir Solid Organ Transplant Study Group. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; 4: 611–20.
6. Khoury JA, *et al.* Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *Am J Transplant* 2006; 6: 2134–43.
7. Said T, *et al.* Oral valgancyclovir versus intravenous gancyclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transplant Proc* 2007; 39: 997–9.
8. Asberg A, *et al.* VICTOR Study Group. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007; 7: 2106–13.
9. Len O, *et al.* RESITRA. Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; 46: 20–7.
10. Asberg A, *et al.* Valganciclovir for the prevention and treatment of CMV in solid organ transplant recipients. *Expert Opin Pharmacother* 2010; 11: 1159–66.
11. Snydman DR. Use of valganciclovir for prevention and treatment of cytomegalovirus disease. *Clin Infect Dis* 2008; 46: 28–9.
12. Humar A, *et al.* The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant* 2010; 10: 1228–37.
13. Humar A, *et al.* Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study. *Transplantation* 2010; 90: 1427–31.
14. Palmer SM, *et al.* Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. *Ann Intern Med* 2010; 152: 761–9.
15. Sun H-Y, *et al.* Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. *Am J Transplant* 2008; 8: 2111–18.

Human herpesvirus-8. Human herpesvirus-8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), causes Kaposi sarcoma (p. 718.1), primary effusion lymphoma (see under AIDS-related Lymphomas, p. 697.2), and some types of multicentric Castleman disease (see under Uses and Administration of Rituximab, p. 853.1). A small randomised, double-blind, placebo-controlled, crossover study[1] in 26 (HIV-infected and non-infected) men with HHV-8 infection found that oral valganciclovir 900 mg daily for 8 weeks significantly reduced HHV-8 oropharyngeal mucosal replication; the frequency with which HHV-8 was detected in the saliva was reduced as was the quantity of HHV-8 detected. However, replication resumed after treatment was stopped. Some have suggested that valganciclovir may have a role in chronic maintenance treatment of Castleman disease.[2]

1. Casper C, *et al.* Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis* 2008; 198: 23–30.
2. Bower M. How I treat HIV-associated multicentric Castleman disease. *Blood* 2010; 116: 4415–21.

Adverse Effects, Treatment, and Precautions

As for Ganciclovir, p. 983.3.

In the USA, valganciclovir is not indicated for use in liver transplant recipients, because of reports of a higher incidence of tissue-invasive CMV infection compared with patients treated with ganciclovir (although see Cytomegalovirus Infections, above). In the UK, valganciclovir is licensed for use in the prevention of CMV disease in all solid organ graft recipients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valganciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/09/11)

Interactions

As for Ganciclovir, p. 984.1.

Antiviral Action

As for Ganciclovir, p. 984.2.

Pharmacokinetics

Valganciclovir is well absorbed from the gastrointestinal tract after oral doses and is rapidly converted to ganciclovir

by first-pass intestinal or hepatic metabolism. The bioavailability of ganciclovir after an oral dose with food is reported to be about 60% and peak plasma concentrations of ganciclovir occur after 1 to 3 hours. Valganciclovir is eliminated in the urine as ganciclovir (see p. 984.2).

References.
1. Brown F, *et al.* Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. *Clin Pharmacokinet* 1999; 37: 167–76.
2. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. *J Clin Pharmacol* 1999; 39: 800–4.
3. Pescovitz MD, *et al.* Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. *Antimicrob Agents Chemother* 2000; 44: 2811–15.
4. Wiltshire H, *et al.* Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; 44: 495–507.
5. Winston DJ, *et al.* Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. *Biol Blood Marrow Transplant* 2006; 12: 635–40.
6. Zhao W, *et al.* Population pharmacokinetics of ganciclovir following administration of valganciclovir in paediatric renal transplant patients. *Clin Pharmacokinet* 2009; 48: 321–8.
7. Caldés A, *et al.* Population pharmacokinetics of ganciclovir after intravenous ganciclovir and oral valganciclovir administration in solid organ transplant patients infected with cytomegalovirus. *Antimicrob Agents Chemother* 2009; 53: 4816–24.
8. Perrottet N, *et al.* Valganciclovir in adult solid organ transplant recipients: pharmacokinetic and pharmacodynamic characteristics and clinical interpretation of plasma concentration measurements. *Clin Pharmacokinet* 2009; 48: 399–418.
9. Pescovitz MD, *et al.* Pharmacokinetics of oral valganciclovir solution and intravenous ganciclovir in pediatric renal and liver transplant recipients. *Transpl Infect Dis* 2010; 12: 195–203.
10. Welker H, *et al.* Ganciclovir pharmacokinetic parameters do not change when extending valganciclovir cytomegalovirus prophylaxis from 100 to 200 days. *Transplantation* 2010; 90: 1414–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Valixa; ***Austral.***: Valcyte; ***Austria***: Valcyte; ***Belg.***: Valcyte; ***Braz.***: Valcyte; ***Canad.***: Valcyte; ***Chile***: Valixa; ***China***: Valcyte (万赛维); ***Cz.***: Valcyte; ***Denm.***: Valcyte; ***Fin.***: Valcyte; ***Fr.***: Rovalcyte; ***Ger.***: Valcyte; ***Gr.***: Valcyte; ***Hong Kong***: Valcyte; ***Hung.***: Valcyte; ***Indon.***: Valcyte; ***Irl.***: Valcyte; ***Israel***: Valcyte; ***Ital.***: Darilin; Valcyte; ***Malaysia***: Valcyte; ***Mex.***: Valcyte; ***Neth.***: Valcyte; Valixa; ***Norw.***: Valcyte; ***NZ***: Valcyte; ***Philipp.***: Valcyte; ***Pol.***: Valcyte; ***Port.***: Rovalcyte; ***Rus.***: Valcyte (Вальцит); ***S.Afr.***: Valcyte; ***Singapore***: Valcyte; ***Spain***: Valcyte; ***Swed.***: Valcyte; ***Switz.***: Valcyte; ***Thai.***: Valcyte; ***Turk.***: Valcyte; ***UK***: Valcyte; ***Ukr.***: Valcyte (Вальцит); ***USA***: Valcyte; ***Venez.***: Valixa.

Pharmacopoeial Preparations
USP 36: Valganciclovir Tablets.

Vidarabine *(BAN, USAN, rINN)*

Adenine Arabinoside; Ara-A; CI-673; Vidarabiini; Vidarabin; Vidarabina; Vidarabinum; Видарабин.

9-β-D-Arabinofuranosyladenine monohydrate.

$C_{10}H_{13}N_5O_4.H_2O$=285.3

CAS — 5536-17-4 (anhydrous vidarabine); 24356-66-9 (vidarabine monohydrate).

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

UNII — FA2DM6879K (vidarabine); 3XQD2MEW34 (anhydrous vidarabine).

Pharmacopoeias. In *US*.

USP 36: (Vidarabine). A white to off-white powder. Very slightly soluble in water; slightly soluble in dimethylformamide. Store in airtight containers.

Vidarabine Phosphate *(BANM, USAN, rINNM)*

Ara-AMP; Arabinosyladenine Monophosphate; CI-808; Fosfato de vidarabina; Vidarabina, fosfato de; Vidarabine 5′-Monophosphate; Vidarabine, Phosphate de; Vidarabini Phosphas; Видарабина Фосфат.

9-β-D-Arabinofuranosyladenine 5′-(dihydrogen phosphate).

$C_{10}H_{14}N_5O_7P$=347.2

CAS — 29984-33-6.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

UNII — 106XV160TZ.

Vidarabine Sodium Phosphate

(BANM, USAN, rINNM)

CI-808 Sodium; Fosfato sódico de vidarabina; Natrii Vidarabini Phosphas; Vidarabina, fosfato sódico de; Vidarabine, Phosphate Sodique de; Натрия Видарабина Фосфат.

9-β-D-Arabinofuranosyladenine 5′-(dihydrogen phosphate) disodium.

$C_{10}H_{12}N_5Na_2O_7P$=391.2

CAS — 71002-10-3.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

UNII — ZEC0WCC7UA.

Uses and Administration

Vidarabine is a purine nucleoside obtained from *Streptomyces antibioticus*. It has been used in the treatment of herpes simplex and varicella-zoster infections (p. 955.2 and p. 956.2), although aciclovir and related drugs are generally preferred.

Vidarabine has been used topically in the treatment of herpes simplex keratitis and keratoconjunctivitis as a 3% ophthalmic ointment.

It has also been used as the sodium phosphate as a 10% gel for the treatment of genital herpes.

Vidarabine was formerly used intravenously in the treatment of severe and disseminated herpes simplex infections and herpes zoster but aciclovir is preferred.

Adverse Effects

Adverse effects that may occur when vidarabine is applied to the eyes include irritation, pain, superficial punctate keratitis, photophobia, lachrymation, and occlusion of the lachrymal duct.

Pharmacokinetics

Systemic absorption does not occur after application of vidarabine to the eye; trace amounts of its principal metabolite hypoxanthine arabinoside (arabinosyl hypoxanthine), and vidarabine, if the cornea is damaged, may be found in the aqueous humour.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Hansikang (汉司康); ***Gr.***: Erpimycin; Tekarin; Virerpin; ***Jpn***: Arasena-A.

Pharmacopoeial Preparations
USP 36: Vidarabine Ophthalmic Ointment.

Zalcitabine *(BAN, USAN, rINN)*

ddC; ddCyd; Dideoxycytidine; NSC-606170; Ro-24-2027; Ro-24-2027/000; Tsalsitabiini; Zalcitabin; Zalcitabina; Zalcitabinum; Zalsitabin; Зальцитабин.

2′,3′-Dideoxycytidine.

$C_9H_{13}N_3O_3$=211.2

CAS — 7481-89-2.

ATC — J05AF03.

ATC Vet — QJ05AF03.

UNII — 6L3XT8CB3I.

NOTE. The code DDC has also been used as a synonym for Ditiocarb, p. 1550.2.

Pharmacopoeias. In *US*.

USP 36: (Zalcitabine). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol, in acetonitrile, in chloroform, and in dichloromethane; slightly soluble in cyclohexane. Store in airtight containers. Protect from light.

Uses and Administration

Zalcitabine is a nucleoside reverse transcriptase inhibitor derived from cytidine with antiviral activity against HIV. It has been used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when zalcitabine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

Zalcitabine is given orally in a dose of 750 micrograms every 8 hours. Doses should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Doses of zalcitabine should be reduced for patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 40 mL/minute: 750 micrograms every 12 hours
- CC less than 10 mL/minute: 750 micrograms every 24 hours

Adverse Effects

The most serious adverse effects of zalcitabine are peripheral neuropathy, which can affect up to one-third of patients, and pancreatitis which is rare, affecting up to about 1% of patients, but which can be fatal. Other severe adverse effects include oral and oesophageal ulceration, hypersensitivity reactions including anaphylaxis, cardiomyopathy and heart failure, lactic acidosis and severe hepatomegaly with steatosis (both potentially life-threatening), and hepatic failure.

Precautions

Zalcitabine should be interrupted or stopped if peripheral neuropathy develops. Neuropathy is usually slowly reversible if treatment is stopped promptly but may be irreversible if treatment is continued after symptoms develop. Zalcitabine should be avoided in patients who already have peripheral neuropathy and used with caution in patients at risk of developing it (especially those with a low CD4+ cell count) or taking other drugs that may cause it (see Interactions, below).

Treatment should be interrupted in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded. Zalcitabine should be permanently withdrawn if pancreatitis develops. Patients with a history of pancreatitis or of raised serum amylase should be monitored closely. Zalcitabine should not be used with other drugs known to cause pancreatitis (see Interactions, below).

Zalcitabine should be used with caution in patients with hepatic impairment and treatment interrupted or stopped if hepatic function deteriorates or there are signs of hepatic damage or lactic acidosis. It should be used with caution in patients with renal impairment, and dosage reductions may be necessary. It should also be used with caution in patients with cardiomyopathy or heart failure.

Complete blood count and biochemical tests should be carried out before treatment starts and at regular intervals throughout therapy.

Handling. Exposure of the skin to zalcitabine and inhalation of zalcitabine powder should be avoided.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zalcitabine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Zalcitabine should not be used with other drugs known to cause pancreatitis (for example intravenous pentamidine). Caution is necessary when zalcitabine is given with other drugs that may cause peripheral neuropathy, such as other nucleoside reverse transcriptase inhibitors, chloramphenicol, dapsone, ethionamide, isoniazid (the clearance of which may also be affected—see p. 313.2), metronidazole, nitrofurantoin, ribavirin, and vincristine. Use of zalcitabine with didanosine is not recommended.

The absorption of zalcitabine is reduced by about 25% when given with aluminium- or magnesium-containing antacids.

Cimetidine, probenecid, or trimethoprim can reduce the renal excretion of zalcitabine, resulting in elevated plasma concentrations. Renal excretion of zalcitabine may also be reduced by amphotericin B, aminoglycosides, or foscarnet, potentially increasing its toxicity.

The antiviral action of zalcitabine may be antagonised by lamivudine and the two drugs should not be used together.

Antiviral Action

Zalcitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

The emergence of zalcitabine-resistant strains of HIV has been reported.

References.
1. Jeffries DJ. The antiviral activity of dideoxycytidine. *J Antimicrob Chemother* 1989; 23 (suppl A): 29–34.

Pharmacokinetics

Zalcitabine is absorbed from the gastrointestinal tract with a bioavailability of greater than 80%. The rate of absorption is reduced if given with food. Peak plasma concentrations in the fasting state occur within about 1 hour. Zalcitabine crosses the blood-brain barrier producing CSF concentrations ranging from 9 to 37% of those in plasma. Binding to plasma proteins is negligible. The plasma elimination half-life is about 2 hours.

Zalcitabine is metabolised intracellularly to the active antiviral triphosphate. It does not appear to undergo any substantial hepatic metabolism and is excreted mainly in the urine, in part by active tubular secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hivid†; ***Gr.***: Hivid; ***Jpn***: Hivid†; ***Mex.***: Arlevid; Hivid; ***Rus.***: Hivid (Хивид); ***Singapore***: Hivid; ***Thai.***: Hivid†; ***Turk.***: Hivid; ***Venez.***: Hivid.

Pharmacopoeial Preparations
USP 36: Zalcitabine Tablets.

Zanamivir *(BAN, USAN, rINN)*

GG-167; GR-121167X; 4-Guanidino-2,4-dideoxy-2,3-dehydro-*N*-acetylneuraminic Acid; Tsanamiviiri; Zanamivirum; Занамивир.
5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-*glycero*-D-*galacto*-non-2-enonic acid.
$C_{12}H_{20}N_4O_7$=332.3
CAS — 139110-80-8.
ATC — J05AH01.
ATC Vet — QJ05AH01.
UNII — L6O3XI777I.

Uses and Administration

Zanamivir is a neuraminidase inhibitor used by inhalation for the treatment and prophylaxis (postexposure and seasonal) of influenza A and B (p. 960.2). For *treatment*, it is given in a dose of 10 mg twice daily for 5 days, starting as soon as possible (within 48 hours) after the onset of symptoms.

Zanamivir is given by inhalation for *postexposure prophylaxis* of influenza A and B in household or close contacts and should be started within 36 hours of exposure. The dose is 10 mg once daily for 10 days. For *seasonal prophylaxis* in a community setting 10 mg once daily may be given for up to 28 days and treatment should start within 5 days of an outbreak.

For details of doses in children, see below.

Administration. Although normally given by inhalation, zanamivir has occasionally been given intravenously[1-3] in doses of 600 mg twice daily to seriously ill patients.

1. Kidd IM, *et al.* H1N1 pneumonitis treated with intravenous zanamivir. *Lancet* 2009; 374: 1036.
2. Gaur AH, *et al.* Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. *N Engl J Med* 2010; 362: 88–9.
3. Härter G, *et al.* Intravenous zanamivir for patients with pneumonitis due to pandemic (H1N1) 2009 influenza virus. *Clin Infect Dis* 2010; 50: 1249–51.

Administration in children. Zanamivir is given by inhalation for the treatment and postexposure prophylaxis of influenza A and B. For *treatment*, children may be given the same dose as adults (10 mg twice daily for 5 days), starting within 36 to 48 hours after the onset of symptoms. In the USA it is approved for those from 7 years of age whereas UK licensed product information permits use from 5 years of age.

Postexposure prophylaxis after close contact with infected patients should be started within 36 hours of exposure. Children from 5 years of age may be given the same dose as adults (10 mg once daily for 10 days). Zanamivir is also used for seasonal prophylaxis in a community setting, and the *BNFC* suggests that during an epidemic this dose may be given for up to 28 days.

Influenza. Reviews.[1-3] For further information on neuraminidase inhibitors (including zanamivir), see Influenza, under Oseltamivir, p. 1007.1.

1. Cheer SM, Wagstaff AJ. Zanamivir: an update of its use in influenza. *Drugs* 2002; 62: 71–106.
2. Fleming DM. Zanamivir in the treatment of influenza. *Expert Opin Pharmacother* 2003; 4: 799–805.
3. Tappenden P, *et al.* Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation. *Health Technol Assess* 2009; 13: 1–246.

Adverse Effects

Inhaled zanamivir has generally been well tolerated. Acute bronchospasm or decline in respiratory function, with some fatalities, has been reported rarely in patients with a history of respiratory disease and very rarely in those with no such history. Other effects that have been noted include nasal symptoms, headache, gastrointestinal symptoms, cough, and bronchitis, but they may be difficult to distinguish from the symptoms of influenza. There have also been rare reports of hypersensitivity reactions, including oropharyngeal oedema and severe skin rashes.

There have been postmarketing reports (mostly from Japan) of neuropsychiatric adverse effects, such as delirium and abnormal behaviour, in patients taking neuraminidase inhibitors such as zanamivir.

Reviews.

1. Freund B, *et al.* Zanamivir: a review of clinical safety. *Drug Safety* 1999; 21: 267–81.
2. Gravenstein S, *et al.* Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Safety* 2001; 24: 1113–25.

Precautions

Zanamivir should be used with caution in patients with chronic respiratory diseases as they may be at increased risk of bronchospasm; if zanamivir use is considered appropriate, patients with asthma or chronic obstructive pulmonary disease should have a fast-acting bronchodilator available during treatment. Patients on maintenance therapy with inhaled bronchodilators should inhale the bronchodilator before zanamivir. Patients experiencing bronchospasm should be advised to stop zanamivir and seek medical attention.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Zanamivir inhalation powder should only be given via the diskhaler device provided by the manufacturer; it should not be given in a nebuliser or mechanical ventilator. Death has occurred when the inhalation powder was dissolved in a solution and given by mechanical ventilation.

Pregnancy. For information on the use of neuramidase inhibitors such as Zanamivir in pregnancy, see Oseltamivir, p. 1007.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zanamivir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Antiviral Action

Zanamivir inhibits the viral surface enzyme neuraminidase (sialidase) which is essential for the release of newly formed viral particles from infected cells, and may facilitate access of virus through mucus to the cell surface. Zanamivir is active against influenza A and B virus replication.

Resistance. For information on the development of resistance to zanamivir and other neuraminidase inhibitors, see under Oseltamivir, p. 1008.1.

Pharmacokinetics

Zanamivir is poorly absorbed after oral doses with a bioavailability of about 2%. Inhaled doses produce high local concentrations in the respiratory tract. About 4 to 20% of the inhaled dose is absorbed producing peak serum concentrations at about 1 to 2 hours. Zanamivir is less than 10% bound to plasma protein. It is not metabolized and the absorbed portion is excreted unchanged in the urine with a serum half-life of 2.6 to 5 hours; unabsorbed drug is excreted in the faeces.

References.

1. Aoki FY, Hayden FG (eds). The pharmacokinetics of zanamivir: a new inhaled antiviral for influenza. *Clin Pharmacokinet* 1999; 36 (suppl 1): 1–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Relenza; ***Austral.***: Relenza; ***Austria***: Relenza; ***Belg.***: Relenza; ***Braz.***: Relenza; ***Canad.***: Relenza; ***China***: Relenza (依乐韦); ***Cz.***: Relenza; ***Denm.***: Relenza; ***Fin.***: Relenza; ***Fr.***: Relenza; ***Ger.***: Relenza; ***Gr.***: Relenza; ***Hong Kong***: Relenza; ***Hung.***: Relenza; ***Irl.***: Relenza; ***Israel***: Relenza; ***Ital.***: Relenza; ***Malaysia***: Relenza; ***Mex.***: Relenza; ***Neth.***: Relenza; ***Norw.***: Relenza; ***NZ***: Relenza; ***Philipp.***: Relenza; ***Pol.***: Relenza; ***Port.***: Relenza; ***Rus.***: Relenza (Реленза); ***S. Afr.***: Relenza; ***Singapore***: Relenza; ***Spain***: Relenza; ***Swed.***: Relenza; ***Switz.***: Relenza; ***Thai.***: Relenza; ***Turk.***: Relenza; ***UK***: Relenza; ***Ukr.***: Relenza (Реленза); ***USA***: Relenza.

Zidovudine *(BAN, USAN, rINN)*

Atsidotymidiini; Azidodeoxythymidine; Azidothymidine; Azidotimidina; AZT; Azydotymidyna; BW-509U; BW-A509U; Compound-S; Tsidovudiini; Zidovudin; Zidovudina; Zidovudinas; Zidovudinum; Zydowudyna; Зидовудин.
3′-Azido-3′-deoxythymidine.
$C_{10}H_{13}N_5O_4$=267.2
CAS — 30516-87-1.
ATC — J05AF01.
ATC Vet — QJ05AF01.
UNII — 4B9XT59T7S.

NOTE. The abbreviation AZT has also been used for azathioprine.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Zidovudine). A white or brownish powder. It shows polymorphism. Sparingly soluble in water; soluble in dehydrated alcohol. Protect from light.

USP 36: (Zidovudine). A white to yellowish powder. Exhibits polymorphism. Sparingly soluble in water; soluble in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Zidovudine is a nucleoside reverse transcriptase inhibitor structurally related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p. 957.2). Viral resistance emerges rapidly when zidovudine is used alone, and it is therefore usually used with other antiretrovirals. It may be used alone to prevent vertical transmission from mother to infant if combination antiretroviral therapy is not available.

Zidovudine is given orally in combination with other antiretrovirals for **treatment** in doses of 250 or 300 mg twice daily. Zidovudine may be given by intravenous infusion of a solution containing 2 or 4 mg/mL over 1 hour for short-term management of patients unable to take it orally. The dose is 1 or 2 mg/kg every 4 hours (equivalent to an oral dose of 1.5 or 3 mg/kg every 4 hours).

For the **prevention** of maternal-fetal HIV transmission (p. 959.1), zidovudine may be given orally to *mothers* after the fourteenth week of pregnancy until the beginning of labour in a dose of 100 mg five times daily. During labour and delivery, zidovudine is given by intravenous infusion in a dose of 2 mg/kg over 1 hour, then 1 mg/kg per hour by continuous infusion until the umbilical cord is clamped. When a caesarean section is planned the intravenous infusion is started 4 hours before the operation.

For details of doses in *infants and children*, including the prevention of maternal-fetal HIV transmission, see below

Blood tests should be carried out regularly as described under Precautions, p. 1026.1. If the white cell count or haemoglobin level fall significantly, the dose should be reduced or, alternatively, treatment interrupted briefly, until there is evidence of recovery. Treatment should be stopped if toxicity is severe and cautiously reintroduced once the bone marrow has recovered. Dosage adjustments may also be necessary in patients with renal (see below) or hepatic impairment.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing zidovudine in combination with lamivudine or with abacavir plus lamivudine are available in some countries.

Administration in children. For the **treatment of HIV infection** in infants and children zidovudine is given orally or intravenously with other antiretroviral drugs. UK licensed product information recommends the following *oral* doses based on body-weight; doses should not exceed the maximum adult dose:

For the oral solution:
- 4 kg up to 9 kg: 12 mg/kg twice daily
- 9 to 30 kg: 9 mg/kg twice daily
- 30 kg or more: 250 or 300 mg twice daily

For the oral capsule:
- 8 to 14 kg: 100 mg twice daily
- 14 to 21 kg: 100 mg in the morning, and 200 mg in the evening
- 22 to 30 kg: 200 mg twice daily
- 30 kg or more: 250 or 300 mg twice daily

In the USA, oral zidovudine is licensed for use in children from 4 weeks of age. Based on body-weight, the same daily mg/kg doses listed above are recommended, given in 2 or 3 divided doses. Alternatively, dosing may be based on body-surface area; a daily dose of 480 mg/m² (in 2 or 3 divided doses) is recommended.

Zidovudine may also be given by *intravenous infusion* in a dose of 80 to 160 mg/m² every 6 hours. An intravenous dose of 120 mg/m² every 6 hours is equivalent to an oral dose of about 180 mg/m² every 6 hours

For the **prevention of maternal-fetal HIV transmission** the newborn infant is given zidovudine 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing for 6 weeks. Neonates unable to receive oral doses are given 1.5 mg/kg by intravenous infusion over 30 minutes every 6 hours. (For doses to be given to the mother for the prevention of maternal-fetal transmission see above.)

Administration in renal impairment. Oral doses of zidovudine should be reduced in patients with severe renal impairment (creatinine clearance less than 10 to 15 mL/minute) and in those on haemodialysis or peritoneal dialysis. Licensed product information gives the following guidance:
- *oral* administration: 100 mg every 6 to 8 hours
- *intravenous* administration: 1 mg/kg every 6 to 8 hours

Adverse Effects

The commonest serious adverse effects reported with zidovudine are haematological toxicities such as anaemia leucopenia, and neutropenia. They occur most often when higher doses are used (1.2 to 1.5 g daily) and in patients with advanced HIV disease and a low CD4+ cell count (less than

100 cells/mm³). These haematological toxicities are usually reversed by interrupting treatment or reducing dosage but the anaemia may be severe enough to require blood transfusion. Aplastic anaemia, pure red cell aplasia, pancytopenia, and thrombocytopenia have been rarely reported.

Other commonly reported adverse effects include dizziness, headache, malaise, myalgia, and gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea, and vomiting. Long-term use of zidovudine has been associated with symptomatic myopathy. Raised liver enzymes, hyperbilirubinaemia, lactic acidosis, and severe hepatomegaly with steatosis have been reported as rare, but potentially fatal, occurrences in patients taking zidovudine alone or with other antiretrovirals. Other rare but potentially serious adverse effects include cardiomyopathy, convulsions, and pancreatitis.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including zidovudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including zidovudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the blood. Bone marrow suppression (in particular anaemia) was the major dose-limiting adverse effect seen in early clinical studies of zidovudine, where the drug was used in total daily doses of 1 to 1.5 g. In these studies, up to 50% of patients developed anaemia or leucopenia[1] sometimes requiring multiple blood transfusions for management.[2] It should be noted, however, that the doses used in modern HAART regimens are typically much lower, and haematological adverse effects consequently occur at a much lower frequency than in these early reports.. Those with more advanced HIV disease, lower CD4+ counts, decreased serum-vitamin B_{12} or -folinic acid concentrations, or baseline anaemia or neutropenia may be at greater risk.[1]

Recombinant erythropoietin has been used in an attempt to reduce the need for blood transfusion in zidovudine-induced anaemia, and measurement of baseline serum-erythropoietin concentrations may help determine which patients will benefit; pooled data from 4 studies[3] suggested that recombinant erythropoietin was effective in reducing the mean transfusion requirement only in patients with endogenous serum-erythropoietin concentrations of 500 units/litre or less. Similarly, use of granulocyte colony-stimulating factor may be of benefit in reducing zidovudine-induced neutropenia (for further information, see under Uses and Administration of Pegfilgrastim, p. 1152.3).

1. McLeod GX, Hammer SM. Zidovudine: five years later. *Ann Intern Med* 1992; 117: 487–501.
2. Richman DD, *et al.* The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. *N Engl J Med* 1987; 317: 192–7.
3. Henry DH, *et al.* Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. *Ann Intern Med* 1992; 117: 739–48.

Effects on the CNS. Reports of adverse effects on the CNS associated with zidovudine include mania,[1,2] seizures[3,4] (following an overdose in one patient[3]), psychogenic panic,[6] and Wernicke's encephalopathy,[7] mostly involving one or two patients in each case. CNS toxicity, thought to be zidovudine-related, contributed to the death of an AIDS patient.[8]

For reports of neurological symptoms associated with mitochondrial dysfunction in infants whose mothers received perinatal zidovudine, see Effects on Mitochondria, below.

1. Maxwell S, *et al.* Manic syndrome associated with zidovudine treatment. *JAMA* 1988; 259: 3406–7.
2. Wright JM, *et al.* Zidovudine-related mania. *Med J Aust* 1989; 150: 339–40.
3. Harris PJ, Caceres CA. Azidothymidine in the treatment of AIDS. *N Engl J Med* 1988; 318: 250.
4. D'Silva M, *et al.* Seizure associated with zidovudine. *Lancet* 1995; 346: 452.
5. Rouzy JP, *et al.* Seizure after zidovudine overdose. *Lancet* 1989; i: 384–5.
6. Levitt AJ, Lippert GP. Psychogenic panic after zidovudine therapy—the therapeutic benefit of an N of 1 trial. *Can Med Assoc J* 1990; 142: 341–2.
7. Davryan DG, Vinters HV. Wernicke's encephalopathy in AIDS patient treated with zidovudine. *Lancet* 1987; i: 919–20.
8. Hagler DN, Prame PT. Azidothymidine neurotoxicity. *Lancet* 1986; ii: 1392–3.

Effects on the heart. An observational study[1] evaluated whether NRTIs increase the risk of myocardial infarction in HIV-infected individuals. Of 33 347 patients enrolled in the D:A:D study, myocardial infarction was reported in 517. Recent use of abacavir or didanosine (but not cumulative use) was associated with an increased rate of myocardial infarction (relative risk 1.90 and 1.49 respectively) compared with those with no recent use of the drugs. The excess risk could not be explained by underlying established cardiovascular risk factors and was not present beyond 6 months after stopping the drug. No associations were found between the rate of myocardial infarction and use of zidovudine, stavudine, or lamivudine.

Subsequent studies exploring the reproducibility of these findings have shown conflicting results. In an analysis of data from 2752 patients enrolled in the SMART study,[2] current use of abacavir was associated with increased risk of cardiovascular disease compared with other NRTIs, including a significantly increased risk of myocardial infarction (hazard ratio of 4.3); didanosine, however, was not found to be associated with increased cardiovascular risk. In contrast, a pooled, post-hoc analysis[3] of 52 manufacturer-sponsored studies (14 174 patients) found no excess risk of myocardial infarction with antiretroviral regimens containing abacavir compared with regimens not containing the drug.

Based on available data, and the lack of an established, biological mechanism explaining the reported risk, the EMEA have concluded that a causal relationship between treatment with abacavir and the risk of myocardial infarction can neither be confirmed nor refuted.[4] However, a subsequent meta-analysis conducted by the FDA did not show any increased risk of myocardial infarction with the use of abacavir.[5]

1. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; 371: 1417–26. Correction. *ibid.*; 372: 292.
2. SMART/INSIGHT and DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008; 22: F17–F24.
3. Brothers CH, *et al.* Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr* 2009; 51: 20–8.
4. MHRA/CHM. Abacavir: risk of myocardial infarction—update from epidemiological studies. *Drug Safety Update* 2009; 2 (12): 4–5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0517716&RevisionSelectionMethod=LatestReleased (accessed 24/11/09)
5. FDA. FDA drug safety communication: safety review update of abacavir and possible increased risk of heart attack (issued 1 March 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245164.htm (accessed 23/03/11)

Effects on the liver. Severe hepatomegaly with steatosis and lactic acidosis has been reported with most NRTIs, but is most commonly seen with didanosine, stavudine, and zidovudine;[1] for further information, see Effects on the Metabolism, below. Zidovudine has also been associated with rare cases of severe, acute hepatitis;[2-4] reversible increases in liver enzymes and rashes were also reported in 2 patients receiving prophylaxis with zidovudine and zalcitabine after exposure to HIV.[5]

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 10 January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 29/03/11)
2. Dubin G, Braffman MN. Zidovudine-induced hepatotoxicity. *Arm Intern Med* 1989; 110: 85–6.
3. Shintaku M, *et al.* Fulminant hepatic failure in an AIDS patient: possible zidovudine-induced hepatotoxicity. *Am J Gastroenterol* 1993; 88: 464–6.
4. Pai VB, *et al.* Acute hepatitis and bleeding possibly induced by zidovudine and ritonavir in an infant with HIV infection. *Pharmacotherapy* 2000; 20: 1135–40.
5. Henry K, *et al.* Hepatotoxicity and rash associated with zidovudine and zalcitabine chemoprophylaxis. *Ann Intern Med* 1996; 124: 855.

Effects on the metabolism. NRTIs, including zidovudine, are known to interfere with lactate production and clearance in the body, leading to a spectrum of possible hyperlactataemia syndromes ranging from asymptomatic, non-acidotic hyperlactataemia, to potentially fatal lactic acidosis with associated hepatic steatosis. The time to onset of toxicity is generally prolonged; in published studies, the median duration of NRTI exposure before diagnosis of lactic acidosis was 9 months (range 3 to 20 months).[1] Effects on lactate metabolism are thought to occur as a consequence of mitochondrial toxicity (see below).[1,2]

In cohort studies, the incidence of lactic acidosis has been reported to range from 1.3 to 3.9 cases per 1000 person-years on antiretroviral therapy,[1] although the incidence may be higher among women and obese patients;[1,3,4] mortality rates of up to 50% have been reported in some case series, particularly where serum-lactate concentrations exceed 10 mmol/litre.[4] In HIV-infected patients, didanosine and stavudine exposure are thought to produce the highest risk of hyperlactataemia, whereas lamivudine,[1] zidovudine,[5] abacavir,[1,6] and tenofovir[1,6] are considered to be safer. There is some evidence that switching to a zidovudine-based antiretroviral regimen may be a safe option for patients who have recovered from stavudine-induced lactic acidosis;[3] relapse is possible, however,[6] and close monitoring is advised.[3]

1. Ogedegbe A-EO, *et al.* Hyperlactataemia syndromes associated with HIV therapy. *Lancet Infect Dis* 2003; 3: 329–37.
2. Arenas-Pinto A, *et al.* Lactic acidosis in HIV infected patients: a systematic review of published cases. *Sex Transm Infect* 2003; 79: 340–3.
3. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis* 2007; 45: 254–60.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 10 January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 29/03/11)
5. Boubaker K, *et al.* Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis* 2001; 33: 1931–7.
6. Castelnuovo B, *et al.* Is it safe to switch from stavudine to zidovudine after developing symptomatic hyperlactatemia? *Afr Health Sci* 2008; 8: 133–4.

Effects on mitochondria. Concern has been expressed[1] over the effects of NRTIs on mitochondria after reports in France[2] of mitochondrial dysfunction in 8 infants whose mothers had received zidovudine alone, or with lamivudine, to prevent vertical transmission of HIV infection during pregnancy. The effects manifested themselves as severe demyelinating neurological disorder in 2 of the 8, both of whom died after about one year of life. Three other infants had seizures, 1 with severe cardiomyopathy and 1 with spastic diplegia, while the remaining 3 were asymptomatic. None were infected with HIV. A study[3] involving echocardiograms performed from birth to 5 years of age in 382 infants without HIV infection (36 with zidovudine exposure) and 58 infants with HIV infection (12 with zidovudine exposure), all of whom were born to HIV-infected women, found, however, that there was no evidence of abnormality in left ventricular structure or function associated with perinatal zidovudine. While it was considered that further assessment of this toxicity was required, it was emphasised that recommendations for zidovudine use during pregnancy should be maintained.[1,2]

The effects of NRTIs on mitochondria have since been extensively reviewed,[4-14] and many of their established adverse effects such as myopathy, neuropathy, hepatotoxicity, lipodystrophy, and the lactic acidosis-hepatic steatosis syndrome have been hypothesised to result from their ability to inhibit mitochondrial DNA polymerase γ, although other mechanisms may also be involved. Zalcitabine, didanosine, and stavudine are thought to have the highest potential for mitochondrial toxicity and lamivudine and abacavir the least.[4]

1. CSM. Antiretroviral drugs in pregnancy and mitochondrial cytopathy in infants. *Current Problems* 1999; 25: 15. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023136&RevisionSelectionMethod=LatestReleased (accessed 22/05/06)
2. Blanche S, *et al.* Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999; 354: 1084–9.
3. Lipshultz SE, *et al.* Absence of cardiac toxicity of zidovudine in infants. *N Engl J Med* 2000; 343: 759–66.
4. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* 2000; 22: 685–708.
5. Loubeyre-Unique C, *et al.* Antirétroviraux et grossesse: cytopathie mitochondriale et analogues nucléosidiques. *Therapie* 2001; 56: 261–6.
6. White AJ. Mitochondrial toxicity and HIV therapy. *Sex Transm Infect* 2001; 77: 158–73.
7. Walker UA, Brinkman K. NRTI induced mitochondrial toxicity as a mechanism for HAART related lipodystrophy: fact or fiction? *HIV Med* 2001; 2: 163–5.
8. Lewis W. Mitochondrial dysfunction and nucleoside reverse transcriptase inhibitor therapy: experimental clarifications and persistent clinical questions. *Antiviral Res* 2003; 58: 189–97.
9. Walker UA. Update on mitochondrial toxicity: where are we now? *J HIV Ther* 2003; 8: 32–5.
10. Lewis W, *et al.* Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. *Nat Rev Drug Discov* 2003; 2: 812–22.
11. Lewis W. Nucleoside reverse transcriptase inhibitors, mitochondrial DNA and AIDS therapy. *Antivir Ther* 2005; 10 (suppl 2): M13–M27.
12. Moyle G. Mechanisms of HIV and nucleoside reverse transcriptase inhibitor injury to mitochondria. *Antivir Ther* 2005; 10 (suppl 2): M47–M52.
13. Cherry CL, *et al.* Mitochondrial toxicity of nucleoside analogues: mechanism, monitoring and management. *Sex Health* 2005; 2: 1–11.
14. Kohler JJ, Lewis W. A brief overview of mechanisms of mitochondrial toxicity from NRTIs. *Environ Mol Mutagen* 2007; 48: 166–72.

Effects on the musculoskeletal system. Myalgia and other adverse effects on the muscle can occur in patients taking zidovudine, although it has sometimes been difficult to determine whether the effects were caused by the drug or by the underlying HIV infection.[1-4] Zidovudine-induced myopathy has been considered to be a distinct condition characterised by the presence of abnormal mitochondria in muscle-biopsy specimens;[2] this view is supported by the fact that the myopathy readily responds to the withdrawal

of zidovudine or to treatment with corticosteroids or other anti-inflammatory drugs.[1-3] For further discussion of the effects of zidovudine on mitochondria, see p. 1025.3.

Arthralgia involving the knees, elbows, ankles, and wrists has been reported in a patient receiving zidovudine.[5]

1. Gertner E, *et al.* Zidovudine-associated myopathy. *Am J Med* 1989; 86: 814–18.
2. Dalakas MC, *et al.* Mitochondrial myopathy caused by long-term zidovudine therapy. *N Engl J Med* 1990; 322: 1098–1105.
3. Till M, MacDonell KB. Myopathy with human immunodeficiency virus type 1 (HIV-1) infection: HIV-1 or zidovudine? *Ann Intern Med* 1990; 113: 492–4.
4. Simpson DM, *et al.* Myopathies associated with human immunodeficiency virus and zidovudine: can their effects be distinguished? *Neurology* 1993; 43: 971–6.
5. Murphy D, *et al.* Zidovudine related arthropathy. *BMJ* 1994; 309: 97.

Effects on the nails. Bluish or brownish discoloration of fingernails and/or toenails has been reported in several patients receiving zidovudine.[1-5] Dark-skinned patients appear to be most commonly affected.[2,4] Occasionally the abnormal pigmentation also involves the skin.[3,5] It has been pointed out that discoloration of nails has occurred in HIV-infected patients without exposure to zidovudine.[6] Painless periungual pyogenic granulomata has been reported in a patient 3 months after starting treatment with a combined antiretroviral regimen of zidovudine, lamivudine, plus efavirenz; one month after the zidovudine and the lamivudine was stopped the lesions had nearly resolved.[7] Paronychia was reported in 12 HIV-infected patients taking lamivudine.[8] In a further report, 6 patients developed paronychia while taking lamivudine with indinavir.[9]

1. Furth PA, Kazakis AM. Nail pigmentation changes associated with azidothymidine (zidovudine). *N Engl J Med* 1987; 107: 350.
2. Vaiopoulos G, *et al.* Nail pigmentation and azidothymidine. *Ann Intern Med* 1988; 108: 777.
3. Merenich JA, *et al.* Azidothymidine-induced hyperpigmentation mimicking primary adrenal insufficiency. *Am J Med* 1989; 86: 469–70.
4. Don PC, *et al.* Nail dyschromia associated with zidovudine. *Ann Intern Med* 1990; 112: 145–6.
5. Bendick C, *et al.* Azidothymidine-induced hyperpigmentation of skin and nails. *Arch Dermatol* 1989; 125: 1285–6.
6. Chandrasekar PH. Nail discoloration and human immunodeficiency virus infection. *Am J Med* 1989; 86: 506–7.
7. Williams LH, Fleckman P. Painless periungual pyogenic granulomata associated with reverse transcriptase inhibitor therapy in a patient with human immunodeficiency virus infection. *Br J Dermatol* 2007; 156: 163–4.
8. Zerboni R, *et al.* Lamivudine-induced paronychia. *Lancet* 1998; 351: 1256.
9. Tosti A, *et al.* Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; 140: 1165–8.

Precautions

Zidovudine should be used with care in patients with anaemia or bone-marrow suppression. Dosage adjustments or treatment interruptions may be necessary and it has been recommended that zidovudine should not be used if the neutrophil count or haemoglobin value is abnormally low. In patients with advanced symptomatic HIV disease taking oral zidovudine, blood tests should be carried out at least every 2 weeks for the first 3 months of treatment and at least monthly thereafter; blood tests should be performed at least every week in those receiving intravenous zidovudine. In patients with early HIV infection blood tests may be performed less frequently (e.g. every 1 to 3 months).

Care is also required in the elderly and in patients with reduced renal or hepatic function who may require reductions in dose. Patients with risk factors for liver disease should be monitored during treatment. Zidovudine is not recommended in patients with moderate to severe liver disease (Child-Pugh scores 7 to 15). Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Patients with hepatitis C receiving interferon alfa and ribavirin may be at special risk and particular care may be necessary in obese patients and in women. Treatment with zidovudine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology.

Zidovudine should not be given to neonates with hyperbilirubinaemia severe enough to need treatment other than phototherapy or with markedly increased aminotransferase concentrations.

Interference with laboratory tests. Raised urinary thymine concentrations in neonates, due to maternal zidovudine treatment, could produce erroneous results in screening tests for inborn errors of metabolism.[1]

1. Sewell AC. Zidovudine and confusion in urinary metabolic screening. *Lancet* 1998; 352: 1227.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zidovudine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Giving zidovudine to pregnant women with HIV infection from 14 weeks of gestation until delivery, and subsequently to the neonate, has been shown to reduce vertical transmission of the infection (see Uses and Administration, p. 1024.3). Studies have shown that zidovudine can be fetotoxic in *animals* when given early in pregnancy; however, limited studies in human pregnancy have revealed no evidence of human teratogenicity[1] and no adverse effects were seen in a group of infants followed for up to 5.6 years.[2] Although licensed product information recommends that zidovudine should not generally be given before 14 weeks of gestation, it is considered by some experts[1] to be the preferred NRTI for use in antiretroviral regimens during pregnancy.

1. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States (issued 29th April, 2009; updated 24th May, 2010). Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf (accessed 19/08/10)
2. Culnane M, *et al.* Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA* 1999; 281: 151–7.

Interactions

Care should be taken when using zidovudine with drugs that are myelosuppressive (such as amphotericin B, co-trimoxazole, dapsone, doxorubicin, flucytosine, ganciclovir, interferon, systemic pentamidine, pyrimethamine, and vinca alkaloids) or nephrotoxic. Drugs that undergo glucuronidation may delay the metabolism of zidovudine but few of these appear to produce clinically important increases in zidovudine plasma concentrations. Increased toxicity and decreased antiretroviral activity has been reported when zidovudine is given with some other antiviral drugs, and pharmacokinetic interactions have been reported with some of anti-infective drugs often used in patients with HIV infection.

Analgesics. There may be an increased risk of haematotoxicity during use of zidovudine with *NSAIDs*.

Decreased zidovudine clearance[1] and increased area under the zidovudine plasma concentration-time curve[2] has been seen in patients receiving *methadone*.

Severe hepatotoxicity has occurred after use of *paracetamol* in a patient taking zidovudine and co-trimoxazole.[3] However, neither short-term[4] nor long-term[5] studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol.

1. Burger DM, *et al.* Pharmacokinetic variability of zidovudine in HIV-infected individuals: subgroup analysis and drug interactions. *AIDS* 1994; 8: 1683–9.
2. Schwartz EL, *et al.* Pharmacokinetic interactions of zidovudine and methadone in intravenous drug-using patients with HIV infection. *J Acquir Immune Defic Syndr* 1992; 5: 619–26.
3. Shriner K, Goetz MB. Severe hepatotoxicity in a patient receiving both acetaminophen and zidovudine. *Am J Med* 1992; 93: 94–6.
4. Sattler FR, *et al.* Acetaminophen does not impair clearance of zidovudine. *Ann Intern Med* 1991; 114: 937–40.
5. Burger DM, *et al.* Pharmacokinetics of zidovudine and acetaminophen in a patient on chronic acetaminophen therapy. *Ann Pharmacother* 1994; 28: 327–30.

Antibacterials. Studies have indicated that the absorption of zidovudine could be reduced by *clarithromycin*.[1] Licensed product information recommends giving zidovudine and clarithromycin at least 2 hours apart since this has been shown to have no overall effect on the bioavailability of zidovudine.[2] Use of *rifampicin* by patients taking zidovudine has been reported to reduce exposure to zidovudine, probably by inducing glucuronidation and amination. Licensed product information for zidovudine has warned that this may result in a partial, or total, loss of efficacy of the drug.[3,4] *Rifabutin* has not been shown to have a marked effect on zidovudine clearance.[5] *Trimethoprim* has been reported[6,7] to decrease the renal clearance of zidovudine by up to 60% with a consequent increase in plasma concentrations, although it was only thought likely to be of clinical significance in patients with hepatic impairment.[7]

For a report of reduced *pyrazinamide* concentrations in patients receiving zidovudine, see p. 346.2.

1. Polis MA, *et al.* Clarithromycin lowers plasma zidovudine levels in persons with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; 41: 1709–14.
2. Vance E, *et al.* Pharmacokinetics of clarithromycin and zidovudine in patients with AIDS. *Antimicrob Agents Chemother* 1995; 39: 1355–60.
3. Burger DM, *et al.* Pharmacokinetic interaction between rifampin and zidovudine. *Antimicrob Agents Chemother* 1993; 37: 1426–31.
4. Gallicano KD, *et al.* Induction of zidovudine glucuronidation and amination pathways by rifampicin in HIV-infected patients. *Br J Clin Pharmacol* 1999; 48: 168–79.
5. Gallicano K, *et al.* Effect of rifabutin on the pharmacokinetics of zidovudine in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1995; 21: 1008–11.
6. Chatton JY, *et al.* Trimethoprim, alone or in combination with sulphamethoxazole, decreases the renal excretion of zidovudine and its glucuronide. *Br J Clin Pharmacol* 1992; 34: 551–4.
7. Lee BL, *et al.* Zidovudine, trimethoprim, and dapsone pharmacokinetic interactions in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1996; 40: 1231–6.

Antiepileptics. Giving *valproic acid* to 6 patients taking zidovudine produced increases in plasma-zidovudine concentrations and the area under the plasma concentration-time curve.[1] The evidence suggested that this was due to reduced glucuronidation of zidovudine. Zidovudine may possibly reduce or increase plasma concentrations of *phenytoin*.

1. Lertora JJL, *et al.* Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. *Clin Pharmacol Ther* 1994; 56: 272–8.

Antifungals. Use of *fluconazole* with zidovudine produced higher serum-zidovudine concentrations, increased the area under the serum concentration-time curve, and prolonged terminal half-life compared with zidovudine alone in a study in 12 patients.[1] Studies *in vitro* suggested that fluconazole could inhibit the glucuronidation of zidovudine; inhibition was also seen with *amphotericin B, ketoconazole,* and *miconazole,* but not with *flucytosine* or *itraconazole*.[2]

1. Sahai J, *et al.* Effect of fluconazole on zidovudine pharmacokinetics in patients infected with human immunodeficiency virus. *J Infect Dis* 1994; 169: 103–7.
2. Sampol E, *et al.* Comparative effects of antifungal agents on zidovudine glucuronidation by human liver microsomes. *Br J Clin Pharmacol* 1995; 40: 83–6.

Antigout drugs. Use of *probenecid* with zidovudine results in increased plasma concentrations and area under the plasma concentration-time curve of zidovudine, probably due to inhibition of glucuronidation;[1] tubular secretion of the glucuronide metabolite is also reduced. A high incidence of adverse effects has been reported in some patients receiving this combination.[2]

1. de Miranda P, *et al.* Alteration of zidovudine pharmacokinetics by probenecid in patients with AIDS or AIDS-related complex. *Clin Pharmacol Ther* 1989; 46: 494–500.
2. Petty BG, *et al.* Zidovudine with probenecid: a warning. *Lancet* 1990; 335: 1044–5.

Antiprotozoals. Use of *atovaquone* with zidovudine produced moderate increases in the zidovudine plasma concentration and area under the plasma concentration-time curve, probably by inhibition of glucuronidation.[1]

1. Lee BL, *et al.* Atovaquone inhibits the glucuronidation and increases the plasma concentrations of zidovudine. *Clin Pharmacol Ther* 1996; 59: 14–21.

Antivirals. Although there is some evidence from studies *in vitro* that *ribavirin* inhibits phosphorylation of zidovudine, and might therefore reduce its antiviral activity, it is unclear whether an interaction of clinical significance occurs; licensed product information for zidovudine does not recommend the combination, but product information for ribavirin varies, with the US product indicating that no clinical effect was seen. However, the combination may increase the risk of anaemia. Zidovudine product information also recommends that the use of zidovudine with *stavudine* be avoided since similar antagonism has been shown *in vitro*.[1] *Interferon alfa* and zidovudine had a synergistic cytotoxicity to bone-marrow progenitor cells.[2] Severe haematological toxicity occurred when zidovudine was added to *ganciclovir* therapy in AIDS patients with CMV retinitis, necessitating substantial dosage reductions or withdrawal of zidovudine in the majority of patients;[3,4] this additive toxicity with ganciclovir may be one reason why patients given zidovudine and ganciclovir do less well than those given zidovudine and foscarnet. Combined therapy with zidovudine and *aciclovir* is not generally associated with additional toxicity[5] but severe fatigue and lethargy were reported in a patient given aciclovir with zidovudine; this did not occur when either drug was given alone.[6] Evidence of a pharmacokinetic interaction between zidovudine and *didanosine* has been conflicting, with reports of no effect,[7] increased,[8] and decreased[9] plasma concentrations of zidovudine. Small reductions in didanosine plasma concentrations have been reported in patients also receiving zidovudine.[10] However, all changes have generally been small and are likely to be of limited clinical significance. Exposure to zidovudine (as measured by peak plasma concentrations and area under the concentration-time curve) was reduced in HIV patients also given *ritonavir,* whereas the pharmacokinetics of ritonavir were not affected by zidovudine;[11] the clinical relevance of this was not known. Modest increases in plasma-zidovudine concentrations occur on use with *lamivudine*. Although this interaction is usually clinically insignificant, profound anaemia has been reported rarely in patients given this combination.[12,13]

1. Havlir DV, *et al.* In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000; 182: 321–5.

2. Berman E, *et al.* Synergistic cytotoxic effect of azidothymidine and recombinant interferon alpha on normal human bone marrow progenitor cells. *Blood* 1989; 74: 1281–6.
3. Millar AB, *et al.* Treatment of cytomegalovirus retinitis with zidovudine and ganciclovir in patients with AIDS: outcome and toxicity. *Genitourin Med* 1990; 66: 156–8.
4. Hochster H, *et al.* Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS: an AIDS Clinical Trials Group study. *Ann Intern Med* 1990; 113: 111–17.
5. Tartaglione TA, *et al.* Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; 35: 2225–31.
6. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; 316: 547.
7. Collier AC, *et al.* Combination therapy with zidovudine and didanosine compared with zidovudine alone in HIV-1 infection. *Ann Intern Med* 1993; 119: 786–93.
8. Barry M, *et al.* Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in patients with the acquired immunodeficiency syndrome. *Br J Clin Pharmacol* 1994; 37: 421–6.
9. Burger DM, *et al.* Pharmacokinetic interaction study of zidovudine and didanosine. *J Drug Dev* 1994; 6: 187–94.
10. Gibb D, *et al.* Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in children with HIV infection. *Br J Clin Pharmacol* 1995; 39: 527–30.
11. Cato A, *et al.* Multidose pharmacokinetics of ritonavir and zidovudine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1998; 42: 1788–93.
12. Hester EK, Peacock JE. Profound and unanticipated anemia with lamivudine-zidovudine combination therapy in zidovudine-experienced patients with HIV infection. *AIDS* 1998; 12: 439–40.
13. Tseng A, *et al.* Precipitous declines in hemoglobin levels associated with combination zidovudine and lamivudine therapy. *Clin Infect Dis* 1998; 27: 908–9.

Antiviral Action

Zidovudine is converted intracellularly in stages to the triphosphate via thymidine kinase and other kinases. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. It has also been shown to possess activity against Epstein-Barr virus and Gram-negative bacteria *in vitro*.

Zidovudine-resistant strains of HIV emerge rapidly during zidovudine therapy and are responsible for the lack of benefit with long-term monotherapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. The emergence of zidovudine-resistant HIV strains in patients receiving long-term therapy with zidovudine has been recognised since 1989.[1,2] The emergence of drug resistance is associated with the duration[3] of treatment with zidovudine, but not the dose,[4] and is attributed to a high frequency of mutations in the HIV reverse transcriptase gene.[3,5] Development of high-level resistance to zidovudine in patients with advanced HIV infection has been associated with rapid disease progression and death.[6] Primary infection with zidovudine-resistant HIV strains has been recorded,[7] as has zidovudine resistance in patients receiving other nucleoside reverse transcriptase inhibitors,[8,9] although it is possible that these patients had unrecorded exposure to zidovudine.[8] **Cross-resistance** with other reverse transcriptase inhibitors has been recorded and, although the use of zidovudine with lamivudine has been reported to delay or reverse the emergence of some mutations conferring zidovudine resistance, dual resistance to zidovudine and lamivudine has occurred.[10] Analysis of the Delta study[11] found no delay in the emergence of zidovudine resistance when used with didanosine or zalcitabine, although circulating concentrations of resistant virus were lower during combination therapy and antiviral activity was apparently not impaired. Nevertheless, it could be anticipated that the use of zidovudine with other antiretrovirals, and particularly the highly active regimens which suppress viral replication to a high degree, could delay the emergence of resistance. The clinical response of patients with previous exposure to multiple regimens could be compromised by the presence of multidrug resistance.[12,13]

1. Larder BA, *et al.* HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 1989; 243: 1731–4.
2. Rooke R, *et al.* Isolation of drug-resistant variants of HIV-1 from patients on long-term zidovudine therapy. *AIDS* 1989; 3: 411–15.
3. Japour AJ, *et al.* Prevalence and clinical significance of zidovudine resistance mutations in human immunodeficiency virus isolated from patients after long-term zidovudine treatment. *J Infect Dis* 1995; 171: 1172–9.
4. Richman DD, *et al.* Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1990; 3: 743–6.
5. Loveday C, *et al.* HIV-1 RNA serum-load and resistant viral genotypes during early zidovudine therapy. *Lancet* 1995; 345: 820–4.
6. D'Aquila RT, *et al.* Zidovudine resistance and HIV-1 disease progression during antiretroviral therapy. *Ann Intern Med* 1995; 122: 401–8.
7. Erice A, *et al.* Brief report: primary infection with zidovudine-resistant human immunodeficiency virus type 1. *N Engl J Med* 1993; 328: 1163–5.
8. Lin P-F, *et al.* Genotypic and phenotypic analysis of human immunodeficiency virus type 1 isolates from patients on prolonged stavudine therapy. *J Infect Dis* 1994; 170: 1157–64.
9. Demeter LM, *et al.* Development of zidovudine resistance mutations in patients receiving prolonged didanosine monotherapy. *J Infect Dis* 1995; 172: 1480–5.
10. Miller V, *et al.* Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapy failure. *J Infect Dis* 1998; 177: 1521–32.
11. Brun-Vézinet F, *et al.* HIV-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the Delta trial. *Lancet* 1997; 350: 983–90.
12. Kavlick MF, *et al.* Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; 177: 1506–13.
13. Shafer RW, *et al.* Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients. *Ann Intern Med* 1998; 128: 906–11.

Pharmacokinetics

Zidovudine is rapidly absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism with a bioavailability of about 60 to 70%. Peak plasma concentrations occur after about 1 hour. Absorption is delayed when given with food, but bioavailability is probably unaffected. Zidovudine crosses the blood-brain barrier producing CSF to plasma ratios of about 0.5. It crosses the placenta and is distributed into breast milk. It has been detected in semen. Plasma protein binding is reported to be 34 to 38%. The plasma half-life is about 1 hour.

Zidovudine is metabolised intracellularly to the antiviral triphosphate. It is also metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine as unchanged drug and metabolite.

Reviews.

1. Acosta EP, *et al.* Clinical pharmacokinetics of zidovudine: an update. *Clin Pharmacokinet* 1996; 30: 251–62.

Neonates. The pharmacokinetics of zidovudine in infants more than 14 days old are reported to be similar to those in adults. After maternal doses the half-life of zidovudine in 7 neonates has been reported to be extended to a mean of 13 hours.[1] In infants given zidovudine, those under 14 days of age had lower total clearance, longer terminal half-life (about 3 hours), and higher bioavailability than older infants.[2] Zidovudine clearance was low and the half-life prolonged to about 7 hours in premature infants.[3]

1. O'Sullivan MJ, *et al.* The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase 1 Acquired Immunodeficiency Syndrome Clinical Trials Group Study (protocol 082). *Am J Obstet Gynecol* 1993; 168: 1510–16.
2. Boucher FD, *et al.* Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr* 1993; 122: 137–44.
3. Mirochnick M, *et al.* Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. *Antimicrob Agents Chemother* 1998; 42: 808–12.

Pregnancy. In a study in 3 pregnant women with HIV infection,[1] the area under the concentration-time curve for zidovudine was reduced and the clearance of an oral dose increased during pregnancy when compared with up to 4 weeks postpartum. These results differed from those reported from another study which reported no differences during or after pregnancy.[2] This latter study, however, used values obtained no later than 48 hours postpartum for comparison, at which time it is unlikely that physiological functions would have returned to the non-pregnant state. Zidovudine and its glucuronide metabolite cross the placenta reaching concentrations in the fetal blood similar to those in maternal blood.[3,4] However, concentrations of zidovudine in the fetal CNS have been reported to be below those required to exert an anti-HIV effect.[5]

1. Watts DH, *et al.* Pharmacokinetic disposition of zidovudine during pregnancy. *J Infect Dis* 1991; 163: 226–32.
2. O'Sullivan MJ, *et al.* The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I Acquired Immunodeficiency Syndrome Clinical Trials Group Study (protocol 082). *Am J Obstet Gynecol* 1993; 168: 1510–16.
3. Gillet JY, *et al.* Petoplacental passage of zidovudine. *Lancet* 1989; ii: 269–70.
4. Chavanet P, *et al.* Perinatal pharmacokinetics of zidovudine. *N Engl J Med* 1989; 321: 1548–9.
5. Lyman WD, *et al.* Zidovudine concentrations in human fetal tissue: implications for perinatal AIDS. *Lancet* 1990; 335: 1280–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Crisazet; Enpert†; Retrovir; Zetrotax; *Austral.*: Retrovir; *Austria*: Retrovir; *Belg.*: Retrovir; *Braz.*: Produvir†; Retrovir; Revirax; Zidovir; *Canad.*: Novo-AZT; Retrovir; *Chile*: Retrovir; *China*: Ai Jian (艾健); Ding Te (鼎特); FeiTe (费特); He Pu Ren (荷普仁); JiuLi (久利); Ke Ai Si (克艾斯); Kedu (克度); Na Xin De (纳信得); Pu Xi Ding (浦希丁); Qi Luo Ke (奇洛克); Retrovir (立妥威); Wei Nuo (伟诺); Zorpex (佐平新); *Cz.*: Retrovir; *Denm.*: Retrovir; *Fin.*: Retrovir; *Fr.*: Retrovir; *Ger.*: Retrovir; *Gr.*: Apo; Retrovir; Virodon; Zidrevir; *Hong Kong*: Retrovir; *Hung.*: Retrovir†; *India*: Lazid; Retrovir; Zidovir; Zilion; Zydowin; *Indon.*: Retrovir; *Irl.*: Retrovir; *Israel*: Retrovir; *Ital.*: Retrovir; *Malaysia*: Retrovir; *Mex.*: Azetavir; Novavir; Pranadox†; Retrovir; Tunivudin†; Zidic-C†; Zynaraam; *Neth.*: Retrovir; *Norw.*: Retrovir; *NZ*: Retrovir; *Philipp.*: Retrovir; *Pol.*: Azovir†; Retrovir; *Port.*: Ambrodil†; Retrovir; *Rus.*: Retrovir (Ретровир); Thymazide (Тимазид); Viro-Z (Виро-ЗЕТ); Zido-H (Зидо-ЗИЧ); Zidovirine (Зидовирин); *S.Afr.*: Dozra; Retrovir; *Singapore*: Retrovir; *Spain*: Retrovir; *Swed.*: Retrovir; *Switz.*: Retrovir; *Thai.*: Antivir; Retrovir; T-ZA†; TO Vir; *Turk.*: Retrovir; *UK*: Retrovir; *USA*: Retrovir; *Venez.*: Retrovir; Zidovir.

Multi-ingredient Preparations. *Arg.*: 3TC Complex; 3TC/AZT†; Ganvirel Duo; Imunoxa Complex†; Kess Complex; Lazinevir; Muvidina; Tridvir; Trilaxis; Trivudin; Ultraviral Duo†; Zetavudin; Zidomuv; *Austral.*: Combivir; Trizivir; *Austria*: Combivir; Trizivir; *Belg.*: Combivir; Trizivir; *Braz.*: Biovir; Zidolam; *Canad.*: Combivir; Trizivir; *Chile*: Combivir; Tridvir; *China*: Combivir (双汰芝); Trizivir (三协唯); *Cz.*: Combivir; Trizivir; *Denm.*: Combivir; Trizivir; *Fin.*: Combivir; Trizivir; *Fr.*: Combivir; Trizivir; *Ger.*: Combivir; Trizivir; *Gr.*: Combivir; Trizivir; *Hong Kong*: Combivir; Trizivir; *Hung.*: Combivir; Trizivir; *India*: Combivir; Cytocom-E; Cytocom-N; Cytocom; Duovir N; Duovir-E; Duovir; Lamda-Z; Lami Plus; Lamsyn-Z; Lamuzid; Lazid-E; Lazid-N; *Irl.*: Combivir; Trizivir; *Israel*: Combivir; Trizivir; *Ital.*: Combivir; Trizivir; *Malaysia*: Combivir; *Mex.*: Combivir; Trizivir; *Neth.*: Combivir; Trizivir; *Norw.*: Combivir; Trizivir; *NZ*: Combivir; Trizivir; *Philipp.*: Combivir; *Pol.*: Combivir; Trizivir; *Port.*: Combivir; Trizivir; *Rus.*: Combivir (Комбивир); Trizivir (Тризивир); *S.Afr.*: Cipla-Duovir; Colamziv; Combivir; Combozil; Lamzid; Lodiz; Retrovir/3TC Post-HIV Exposure; Sonke Abadamizid; Trizivar; *Singapore*: Combivir; Trizivir; *Spain*: Combivir; Trizivir; *Swed.*: Combivir; Trizivir; *Switz.*: Combivir; Trizivir; *Thai.*: Combid; GPO-Vir Z; Zilavir; Zovilam; *Turk.*: Combivir; Trizivir; *UK*: Combivir; Trizivir; *USA*: Combivir; Trizivir; *Venez.*: Combivir; Duovir; Trizivir.

Pharmacopoeial Preparations

BP 2014: Zidovudine and Lamivudine Tablets; Zidovudine Capsules; Zidovudine Tablets;

USP 36: Lamivudine and Zidovudine Tablets; Zidovudine Capsules; Zidovudine Injection; Zidovudine Oral Solution; Zidovudine Tablets.

Anxiolytic Sedatives Hypnotics and Antipsychotics

The drugs in this chapter include:
- anxiolytic sedatives, formerly called minor tranquillisers, which have been used in the management of anxiety disorders
- drugs used to produce sleep (hypnotics)
- drugs used in the treatment of psychoses (antipsychotics, formerly called major tranquillisers). The term neuroleptic is sometimes used to describe those antipsychotics that have effects on the extrapyramidal system

The difference in action between anxiolytics and hypnotics is mainly one of degree and the same drug or group of drugs can have both effects, larger doses being necessary to produce a state of sleep.

The benzodiazepines (typified by Diazepam, p. 1063.2) replaced the barbiturates (typified by Amobarbital, p. 1037.2) and related sedatives as the major group of drugs used as anxiolytics and hypnotics. Some benzodiazepines are also used for their muscle relaxant and anticonvulsant properties. Newer anxiolytics include buspirone (p. 1042.1), a drug that affects serotonin neurotransmission.

The classical antipsychotics (typified by Chlorpromazine, p. 1045.2) include the butyrophenones, the diphenylbutylpiperidines, the indole derivatives, the phenothiazines, and the thioxanthenes. Some newer antipsychotics such as clozapine (p. 1057.3), risperidone (p. 1103.2), olanzapine (p. 1089.3), quetiapine (p. 1101.1), and amisulpride (p. 1036.3) are often referred to as atypical antipsychotics because of their reduced tendency to cause the extrapyramidal effects typical of classical antipsychotics.

Anxiety disorders

Anxiety is an emotional condition characterised by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating, and tremor. It can be a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are difficult to define and various classifications exist:
- in **acute stress disorder** anxiety is associated with a recent extremely stressful event such as bereavement, and is likely to resolve within a few weeks
- in **generalised anxiety disorder** there is persistent pervasive anxiety and worry, usually lasting 6 months or more, resulting in distress or marked difficulty in performing daily tasks. Symptoms include fatigue and disturbed sleep, motor tension, autonomic hyperactivity, irritability, and loss of concentration

The first step in the **management** of anxiety that cannot be attributed to an underlying disease is the use of psychological treatments such as cognitive therapy. Such therapy can be effective in most types of anxiety. If unsuccessful, short-term treatment with a benzodiazepine may be considered.[1] Benzodiazepines exert an effect very rapidly, possibly even after the first dose, and this makes them suitable for treating an acute reaction.[2] However, their use in chronic conditions such as generalised anxiety disorder is limited by serious problems of dependence (see under Diazepam, p. 1065.1). Tolerance may develop to the anxiolytic effects of benzodiazepines although this appears to be less likely than tolerance to the psychomotor effects. No one benzodiazepine appears more effective than the others in the treatment of anxiety disorders.[3] However, adverse effects and pharmacokinetic parameters may influence choice.

Buspirone, an azaspirodecanedione, appears to have broadly similar efficacy to the benzodiazepines but a slower onset of action; it may cause less sedation and dependence. It is reported to lack euphoriant effect. Its efficacy is reduced in patients who have had previous extensive use of benzodiazepines.[4,5]

Increasingly, antidepressants are considered preferable to benzodiazepines for the treatment of generalised anxiety disorder;[1,2,4,6-12] they are particularly appropriate when medium or long-term therapy is necessary or when depression is also present. They may take several weeks to have an effect, so combined therapy with benzodiazepines may be required initially. Tricyclic antidepressants such as imipramine have a proven benefit in the treatment of generalised anxiety disorder.[2-4,6-8] SSRIs are an alternative;[3,12-14] escitalopram and paroxetine are often used. The noradrenaline and serotonin reuptake inhibitor venlafaxine may also be used.[1,8,12] These relatively newer drugs are safer in overdose and are associated with less severe adverse effects than the tricyclics and in the UK NICE[1] and others[9,11] consider SSRIs to be the antidepressants of choice in generalised anxiety disorder.

Beta blockers may be useful for the control of the physical symptoms of anxiety.[14] There is little evidence to support the efficacy of antihistamines such as hydroxyzine in anxious patients,[2] and the *BNF* considers the use of antihistamines solely for their sedative effect in anxiety to be inappropriate. Antipsychotics have been used by some in severe anxiety for their sedative effects; long-term use should be avoided because of the risk of tardive dyskinesia. Antiepileptics such as pregabalin and tiagabine have been found to be effective for the treatment of generalised anxiety disorder.[15]

Anxiety may be present with other disorders such as depression in **mixed anxiety and depressive disorders**, the management of which is discussed under Depression on p. 398.1.

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Obsessive-compulsive disorder. Obsessive-compulsive disorder is associated with intrusive, recurrent, obsessional thoughts and/or repetitive compulsive behaviour (e.g. hand washing) performed in a ritualistic manner. A combination of pharmacological, behavioural, and psychosocial methods appears to have the most successful long-term outcome in its treatment. **Drug therapy** is based on antidepressants that inhibit reuptake of serotonin.[1-12] These include clomipramine, the SSRIs, and the serotonin and noradrenaline reuptake inhibitor venlafaxine. There is some evidence that clomipramine is more effective than the SSRIs but its adverse effects are more problematic.[3,5,13] In the UK NICE considers SSRIs to be the antidepressants of choice in obsessive-compulsive disorder;[8] similar recommendations are also made in some US[10] and international[11] guidelines. It may take 4 to 6 weeks before any response is obtained and up to about 12 weeks to achieve an optimal effect.[2,10,14] If one serotonin reuptake inhibitor fails then another can be tried;[2-5,8,10] for example, it has been suggested that patients who fail to respond to trials with two SSRIs might then try switching to a drug from a different class (e.g. clomipramine or venlafaxine).[6] Treatment should be continued for at least 12 months in those who respond.[8] However, about 40 to 60% of patients do not respond to these drugs and of those who do, many do not achieve complete remission.[3] Also of those who do respond, many relapse when drug therapy is withdrawn and prolonged or even life-long therapy may be necessary;[7,14] however, long-term efficacy and tolerability of serotonin reuptake inhibitors in obsessive-compulsive disorder has yet to be established.[15] It has been suggested that patients may be maintained on reduced dosage[16] but the optimum dosage remains uncertain.[7] Gradual withdrawal over several months may be more successful if patients are also receiving behavioural therapy.[5]

Drugs such as buspirone, lithium, pindolol, and some antipsychotics including the atypicals have been tried as **adjuncts** when patients are refractory to serotonin reuptake inhibitors and behavioural therapy but results of such augmentation therapy have been variable.[2-7] NICE recommends adding an antipsychotic to an SSRI or clomipramine, or using clomipramine with citalopram in such patients.[8] Intravenous clomipramine has been tried in patients refractory to augmentation therapy.[6]

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Panic disorder. Panic disorder is characterised by severe, sudden, unexpected, recurrent exacerbations of anxiety (panic attacks). During an attack there is a feeling of fear, terror, and impending doom or even death accompanied by autonomic symptoms. Attacks are followed by persistent worry (for at least 1 month) about further attacks and their consequences.

If behavioural or cognitive therapy fails in the management of panic disorder, drug therapy can then be tried but it may need to be prolonged as there is a high rate of relapse on withdrawal.[1] Antidepressants are the drugs of choice in the treatment of panic disorder. While some also consider the combination of psychotherapy with antidepressant therapy to be first-line treatment for panic disorder[2] others consider that a clear benefit of using cognitive behavioural therapy with drug treatment has not yet been shown.[3] Tricyclic antidepressants or SSRIs can reduce the frequency of panic attacks and can often prevent them completely.[4-7] Efficacy is broadly comparable, although SSRIs may be associated with a lower incidence of serious adverse effects.[3,7-11] In the UK NICE considers SSRIs to be the drugs of first choice in panic disorder;[12] US guidelines[3] consider SSRIs and the serotonin and noradrenaline reuptake inhibitor venlafaxine to be the drugs of first choice. Clomipramine or imipramine may be tried as second-line treatments.[12] MAOIs such as phenelzine are also effective but dietary restrictions and serious adverse effects limit their use to patients unresponsive to tricyclics and SSRIs.[3,6]

It may take several weeks before the effects of antidepressants are seen and initially there may be an increase in anxiety and the frequency of panic attacks. Benzodiazepines are sometimes used as adjuncts until antidepressants exert their full effect.[3,6-9,11] Short courses of benzodiazepines may also be of use in patients who cannot tolerate, or who are refractory to, antidepressants.[4] However, any benefit may be outweighed by the risk of dependence[5] and NICE does not recommend their use in the treatment of panic disorder.[12] There is little evidence to support the use of beta blockers, but they may control physical symptoms. Other drugs that may produce beneficial effects in some patients include valproate[4,6,8,13] and possibly clonidine.[14]

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Phobic disorders. Phobic disorders consist of an irrational or exaggerated fear of, and a wish to avoid, specific objects, activities, or situations. As there is a strong link between **agoraphobia** and panic disorder (see above) it is treated similarly. Simple or specific phobias are usually unresponsive to pharmacotherapy and respond better to behavioural therapy, although paroxetine or benzodiazepines may be considered for disabling phobias unresponsive to such measures.[1]

SSRIs, particularly paroxetine, are considered to be the drugs of choice for the treatment of **social anxiety disorder** (social phobia).[1-6] The serotonin and noradrenaline reuptake inhibitor venlafaxine is also used.[1] A systematic review and meta-analysis[7] found evidence to support the efficacy of escitalopram, fluvoxamine, paroxetine, sertraline, and venlafaxine in the treatment of social anxiety disorder; efficacy was found to be similar between these drugs although adverse reaction profiles are known to be different. MAOIs such as phenelzine are effective in social anxiety disorder and can improve anticipatory anxiety and functional disability;[8,9] however, a systematic review found them to be less consistently effective than the SSRIs,[10] and their use is limited by dietary restrictions and serious adverse effects. Results with the reversible inhibitor of monoamine oxidase moclobemide have been variable.[2-5,10] The benzodiazepines bromazepam and clonazepam have been reported to be of some benefit,[1,2,4,5,8,11] although benzodiazepines should be used with caution because of the risk of dependence and abuse. Other drugs being investigated for the treatment of social anxiety disorder include gabapentin and pregabalin.[1,12]

Beta blockers may help to reduce the physical symptoms in **performance-related anxiety**.[4,8,11]

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Post-traumatic stress disorder. In post-traumatic stress disorder (PTSD), anxiety is precipitated by persistent recall of a traumatic experience that was exceptionally threatening or catastrophic in nature. Patients may also suffer from negative symptoms such as avoidance, alienation, emotional numbness, and social withdrawal. The main treatment is psychotherapy.[1-6] Drug therapy is largely aimed at accompanying symptoms of anxiety or depression.[7] The combination of both methods of therapy is preferred for severe cases.[8] Negative symptoms are usually resistant to pharmacotherapy. Some 8 to 12 weeks of treatment is generally thought necessary to judge the efficacy of treatment.[2,3]

SSRIs are the drugs of choice for most of the symptoms of PTSD.[1-3,6,8-13] Tricyclic antidepressants or, in refractory patients, MAOIs, may be used as alternatives to SSRIs to help reduce traumatic recollections and nightmares, and to repress flashbacks.[1-3,9] The newer antidepressants nefazodone and venlafaxine have also been tried,[1-3,9] generally in patients refractory to SSRIs, and some consider these drugs to be more suitable alternatives than tricyclics or MAOIs, which may have serious adverse effects.[10] Atypical antipsychotics have been studied as monotherapy and as adjuncts when patients are refractory to SSRIs; they may also be considered where paranoia or flashbacks are prominent.[10]

In the UK NICE[3] recommends the use of paroxetine, mirtazapine, amitriptyline, or phenelzine in patients who refuse psychotherapy, where psychotherapy is inappropriate or ineffective, or as adjunctive therapy in those with significant comorbid depression or severe hyperarousal. In patients who do not respond, further drug therapy may be considered with a different class of antidepressant or adjunctive olanzapine. Drug therapy should be continued for at least 12 months in responders before gradual withdrawal.

It has been suggested that antiepileptics should be considered in those with comorbid bipolar disorder, and where impulsivity and anger predominate.[10] Carbamazepine and valproate appear to improve symptoms of hyperreactivity, violent behaviour, and angry outbursts but only a small number of patients have been studied.[9,10,14] Lamotrigine may also relieve avoidance and intrusive symptoms although, again, patient numbers are small.[9,14]

Benzodiazepines may be helpful for short-term management of anxiety and sleep disturbances (although some studies have failed to show benefit[7]) but they must be used with caution because of the risk of dependence and abuse,[1,10,11] and the possibility of worsening PTSD;[11] some do not favour their use, even short-term.[3,6] In several small studies, prazosin has been found to be a promising and fairly well-tolerated drug in the management of sleep-related symptoms.[13,15]

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Extrapyramidal disorders

Extrapyramidal disorders are movement disorders involving the brain's motor systems outside the pyramidal tract. They are usually characterised by akinesia (a loss of movement) or bradykinesia (abnormal slowness of movement) accompanied by an increase in muscle tone (typified by parkinsonism, p. 889.1); or by dyskinesias (abnormal involuntary movements), often accompanied by a reduction in muscle tone (see below for some examples). Drug-induced extrapyramidal disorders are discussed under Chlorpromazine, p. 1049.2.

Ballism. Ballism, sometimes called hemiballism or hemiballismus because it is usually unilateral, consists of involuntary flinging movements of the extremities and most often results from acute vascular infarction or haemorrhage of the subthalamic nucleus. It often improves spontaneously but dopamine-blocking antipsychotics such as haloperidol or dopamine-depleting drugs such as tetrabenazine may be needed to control severe symptoms. Surgery may be necessary in severe cases.

Chorea. Chorea is characterised by brief involuntary muscle contractions and an inability to sustain voluntary contractions. It may be related to neurological abnormalities in the caudate nucleus and putamen of the striatum as well as other basal ganglia structures. Overactivity of dopaminergic nigrostriatal pathways and depletion of gamma-aminobutyric acid (GABA) and acetylcholine may also play a part. Chorea may be an adverse effect of some drugs, including antipsychotics, levodopa, and oral contraceptives; it may also be a symptom of an underlying disorder such as SLE.

Huntington's chorea (Huntington's disease, progressive hereditary chorea) is a hereditary autosomal dominant disease characterised by chorea, behavioural disturbances, and a progressive decline in cognitive function culminating in dementia and death. The identification of a gene marker for Huntington's chorea now makes it possible to identify carriers of the abnormal gene.[1-4] Symptoms usually appear in mid-life, with death following after about 15 years, although there are also juvenile-onset forms. Westphal variant, a form commonest in children, tends to be characterised more by rigidity than by chorea.[1]

Sydenham's chorea (St Vitus' dance; chorea minor) is an acute, usually self-limiting, disorder with an autoimmune basis, characterised by chorea and behavioural disturbances. It commonly occurs about 6 months after rheumatic fever but is now rare since the incidence of

rheumatic fever has declined. It may also arise during pregnancy (chorea gravidarum).

Treatment of chorea is symptomatic only and does not alter the progressive decline of Huntington's chorea;[1-7] Sydenham's chorea resolves spontaneously within weeks or months but antibacterial prophylaxis to prevent recurrence of rheumatic fever (p. 202.3) has been recommended. Other forms of chorea may resolve with treatment of the underlying disorder or withdrawal of any causative drug.

Tetrabenazine has been used effectively in chorea, although not all patients respond, and it may produce depression.[1-3,7] Nevertheless, tetrabenazine was found to be the drug with the best available clinical evidence in the symptomatic treatment of Huntington's chorea.[4-6] The mode of action is thought to involve depletion of striatal dopamine.[2] Reserpine, which has a similar action and effects, has also been used but is limited by its adverse effects.[2]

Phenothiazines such as fluphenazine[2] have dopamine-receptor blocking activity and have also been used to treat chorea. Other antipsychotics with a similar mode of action that have been used include haloperidol,[1,2,4] pimozide,[2] and sulpiride.[1,2,4] Some atypical antipsychotics[2,4,7] such as olanzapine, quetiapine, risperidone, and zotepine have also been tried. Adverse effects such as tardive dyskinesias may limit the use of antipsychotics,[1,2] and doses should be kept as low as possible;[2] attempts to control choreiform movements completely are not recommended. In addition to improving chorea, antipsychotics may also be of value in controlling the behavioural symptoms associated with Huntington's chorea; anxiolytics and antidepressants may also be of use.[1,2]

Carbamazepine[1] has been tried with some degree of success in a limited number of patients. The use of drugs to increase GABA activity has been of little value.[2] Other drugs being investigated include amantadine,[3] minocycline,[2,3] and ubidecarenone.[1-3] Implantation of human and porcine fetal neural cells is being studied,[1] as are various forms of gene therapy.

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Tics. Tics may manifest as sudden, involuntary, brief, isolated, repetitive movements, both simple (e.g. eye blinking, nose twitching, or head jerking) and complex (e.g. touching, jumping, or kicking); they may also be sensory in nature or may present in a vocal or phonic way and can range from simple clearing of the throat to more complex symptoms such as echolalia (involuntary repetition of others speech) or coprolalia (involuntary and inappropriate swearing). Symptoms can usually be suppressed voluntarily and may increase with stress and decrease with distraction.[1-3] Some tics persist during sleep.[2,3] The most common cause is **Tourette's syndrome** (Gilles de la Tourette's syndrome), in which behavioural disturbances usually accompany the tics.[1-5] It is a genetic disorder with an onset during childhood and is characterised by recurrent multiple motor and vocal tics that are not due to the direct physiological effects of a substance or a medical condition, with a duration of at least 1 year.

Most patients' symptoms wax and wane and behavioural therapy and reassurance may be sufficient to resolve mild tics.[1,2] Drug treatment may be necessary if tics are severe enough to cause discomfort or embarrassment.[1,2,4,6] Clonidine[1,5-7] or guanfacine[1,5-7] are increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects. For more severe cases the classical antipsychotics pimozide or haloperidol have been widely tried[3,8] to decrease the frequency and severity of tics, and may improve any accompanying behavioural disturbances; however, the risk of developing serious adverse effects such as tardive dyskinesia should be balanced against the perceived benefits of treatment.[8] Pimozide may be slightly less effective than haloperidol, but adverse effects are less frequent.[9] Other antipsychotics such as fluphenazine, sulpiride, or tiapride have also been tried;[4,6,8] increasingly, atypical antipsychotics, notably risperidone but also including olanzapine, quetiapine, and ziprasidone, are preferred because their adverse effect profile is seen as more acceptable.[7] Doses should be as low as possible, bearing in mind that optimum treatment does not necessarily lead to the complete control of symptoms.[2,4]

Other drugs[1-4,6,8] that may be used in the management of tics and/or behavioural aspects of Tourette's syndrome include baclofen, botulinum toxin, clonazepam, levodopa, pergolide, and tetrabenazine. Nicotine has been reported to produce benefit when used alone or with haloperidol in patients whose symptoms were not satisfactorily controlled with haloperidol alone.[7,10]

For drugs used in the treatment of comorbid disorders commonly associated with Tourette's syndrome, such as obsessive-compulsive disorder and attention deficit hyperactivity disorder, see p. 1028.2 and p. 2314.1, respectively.

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Hypochondriasis

Hypochondriasis (hypochondriacal neurosis) is a morbid preoccupation with one's health characterised by a fear or belief that normal bodily sensations are indicative of serious disease. It persists despite medical reassurance and management is difficult. If hypochondriasis is secondary to a psychiatric disorder, particularly depression and some anxiety disorders, treatment aimed at the primary condition may also lead to resolution of the hypochondriacal symptoms.[1-3]

Cognitive and behavioural therapies may be useful in the treatment of hypochondriasis; drug treatment of primary hypochondriasis has been less well studied although antidepressants such as the SSRIs may be effective.[1-4] Pimozide is used in the management of hypochondriacal psychoses such as delusions of parasitic infestation.[5] Atypical antipsychotics such as quetiapine and risperidone have been used as alternatives to pimozide in the treatment of delusional parasitosis.[6-8] A systematic review[7] did not find any randomised controlled studies on the use of classical or atypical antipsychotics in the treatment of delusional parasitosis but tentatively concluded that, based on weak evidence, antipsychotics are effective in treating primary delusional parasitosis. Pimozide had the best evidence of efficacy but its use is limited by its more problematic adverse effects.

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Psychoses

Psychoses and psychotic disorders are terms that have been used to describe a collection of severe psychiatric disorders in which the patient has disordered thinking and loses contact with reality due to delusions and/or hallucinations. There may be accompanying mood or behavioural disturbances. *Organic psychoses* arise from organic brain disease produced by toxic insults, metabolic disturbances, infections, or structural abnormalities and may be acute (delirium) or chronic (dementia) in nature.

Disturbed behaviour. Drug therapy is sometimes indicated for the immediate control of severely disturbed, agitated, or violent behaviour associated with a variety of conditions such as toxic delirium, brain damage, mania (see Bipolar Disorder, p. 397.2), or other psychotic disorders. In the UK NICE has issued guidelines on the short-term management of disturbed or violent behaviour in adults.[1] Antipsychotics and benzodiazepines, either alone or in combination, are commonly used for disturbed behaviour. There is little agreement on the best antipsychotic for these indications, selection depending mainly on the condition of the patient and the adverse effect profile of the drug.[2-9] Oral therapy should be tried first and parenteral therapy only given if this is ineffective or refused. The high-potency butyrophenone haloperidol is commonly used for **acutely disturbed behaviour** although it lacks any sedative effects and may be associated with severe extrapyramidal adverse effects. The atypical antipsychotics such as olanzapine and risperidone are increasingly used in acute situations. A systematic review,[10] albeit of 3 small studies, concluded tentatively that there was no difference in efficacy and incidence of adverse effects between low-dose haloperidol and olanzapine or risperidone in the management of delirium; high-dose haloperidol was associated with a greater incidence of extrapyramidal effects. Benzodiazepines such as diazepam and lorazepam are valuable sedatives for the disturbed or delirious patient. A combination of an antipsychotic and a benzodiazepine allows the use of lower doses of each drug. However, a systematic review[11] considered that there were insufficient data to support or refute the use of benzodiazepines, either alone or with an antipsychotic, in the treatment of acute psychosis. Another systematic review[12] found the combination of haloperidol and the antihistamine promethazine, both given intramuscularly, to be effective.

Other drugs that have had some success in the control of symptoms such as agitation, aggression, rage, or violent behaviour include beta blockers, lithium, carbamazepine, and valproate. Buspirone and antidepressants such as the SSRIs and trazodone may also be useful.

Antipsychotics appear to be modestly effective for the control of disturbed behaviour associated with the **dementia** of chronic conditions such as Alzheimer's disease (p. 388.1).[13-18] However, antipsychotics can themselves precipitate confusion or exacerbate dementia and may hasten cognitive decline, increase the risk of falls, incontinence, and drowsiness, and interfere with the performance of motor skills.[19] Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotics and the reaction can be life-threatening. In 2005, the FDA[20] was aware of placebo-controlled studies that showed an increased risk of mortality with the use of the atypical antipsychotics aripiprazole, olanzapine, quetiapine, and risperidone in elderly patients with dementia; most of the deaths appeared to be due to cardiovascular events or infection. The FDA considered it likely that the atypicals as a group were associated with an increased risk of death in such patients (for further details, see the Elderly, under Risperidone, p. 1105.1). After a further review, in 2008, of 2 observational studies in elderly patients, the FDA[21] concluded that both classical and atypical antipsychotics were associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis (for more details, see the Elderly, under Chlorpromazine, p. 1051.1). Methodological limitations precluded any conclusion that classical antipsychotics have a greater mortality risk than atypical antipsychotics.

Antipsychotics are used only after careful consideration of the causes of disturbed behaviour and the benefits and risks of antipsychotic treatment. Very low doses are given at first and increased gradually according to clinical response and development of adverse effects; the necessity for continued use is reviewed periodically. Again, there is no agreement over the choice of antipsychotic. A systematic review noted that while there was limited evidence to support the routine use of haloperidol for agitation in dementia, it appeared to reduce aggression.[22] Atypical antipsychotics such as olanzapine, quetiapine, and risperidone may be less likely to produce extrapyramidal effects, but cerebrovascular adverse effects are a problem. The UK CSM recommended[23] in 2004 that risperidone and olanzapine should not be used to treat behavioural problems in elderly patients with dementia after analysis of placebo-controlled clinical studies revealed an increased risk of stroke with these 2 atypical antipsychotics (but see below). Guidelines for the management of behavioural and psychiatric symptoms in patients with dementia and a history of stroke or transient ischaemic attacks issued in the UK[24] state that consideration should be given to the withdrawal of existing olanzapine and risperidone therapy and starting treatment with a classical antipsychotic or an atypical that has not been associated with an increased risk of cerebrovascular adverse effects. A large multicentre study[25] concluded that adverse effects of atypical antipsychotics (olanzapine, quetiapine, and risperidone) outweigh their benefits in treating behavioural disturbances in patients with Alzheimer's disease. A long-term placebo-controlled study[26] in patients with Alzheimer's disease given antipsychotics (chlorpromazine, haloperidol, risperidone, thioridazine, or trifluoperazine) also concluded that, for most patients, stopping antipsychotic therapy had no overall detrimental effect on functional and cognitive status. The authors suggested that although antipsychotics may have some value in the maintenance treatment of more severe behavioural disturbances, any potential benefits must be weighed against the risk of serious adverse effects. During follow-up[27] a higher mortality rate was found in the patients who continued to receive antipsychotics compared with those who stopped antipsychotic therapy; most patients were taking risperidone or haloperidol. The authors

noted that antipsychotics should only be used for short periods in the treatment of severe neuropsychiatric symptoms, particularly aggression, in this patient group. In 2009, the UK CHM[28] stated that analysis of 3 randomised studies showed a clear benefit for the short-term use of risperidone in the treatment of aggression in elderly patients with dementia; risperidone is now licensed for such use in the UK.

The sedative drug, clomethiazole, may be a useful alternative to antipsychotics for the control of agitated behaviour in elderly patients, generally causing fewer adverse effects; respiratory depression, excessive sedation, and dependence may, however, be a problem. Benzodiazepines are not generally indicated for the management of elderly demented patients because of the risks of dependence with continued use, disinhibiting effects, and the particular problems of these drugs in old people (see the Elderly, under Diazepam, p. 1067.2). They are not as effective as antipsychotics in reducing behavioural problems, but may be useful in short courses for the management of severe anxiety disorders, or given as required for patients who only have rare episodes of agitation.

The use of antipsychotics in the control of **disturbed behaviour in children** is controversial and can probably be justified only in severe cases resistant to non-pharmacological therapy.[29-31] Aggression in children (with autism, conduct disorder, and mental retardation) has been treated with antipsychotics on a short-term basis. High-potency classical antipsychotics such as haloperidol may be less likely to cause sedation or impair arousal, cognitive function, and learning. Atypical antipsychotics such as olanzapine and risperidone have been used for the control of aggression in children with autism and conduct disorder but are associated with weight gain.[30-32] Nonetheless, in some countries, including the USA, aripiprazole and risperidone are licensed for the treatment of irritability associated with autistic disorder in children and adolescents; in the UK, risperidone is licensed for the short-term treatment of persistent aggression in conduct disorder in children and adolescents with subaverage intellectual functioning or mental retardation. Quetiapine and ziprasidone have also been tried in the treatment of behavioural disturbances associated with autistic disorder.[32,33] The tendency of antipsychotics to lower the seizure threshold is an important consideration in autistic children who are at an increased risk of seizure disorders. Other drugs that have been tried include clonidine, lithium, and the SSRIs.[30,31] Guidance on the management of autism spectrum disorders has been issued by the American Academy of Pediatrics.[34]

Antipsychotics have been used to control the symptoms of **drug-induced psychosis** in patients with Parkinson's disease.[35-37] Initially, other possible causes such as infections or metabolic and endocrine changes should be eliminated.[36] If psychotic symptoms persist, antiparkinsonian drugs should be gradually stopped or used at the lowest effective dose. Treatment of sleep disturbances in these patients may reduce psychosis; low doses of sedating antidepressants, such as mirtazapine, nortriptyline, or trazodone, are preferable to benzodiazepines or antihistamines which may contribute to confusion and psychosis.[37] Psychosis may be particularly difficult to treat, since the extrapyramidal effects of classical antipsychotics can exacerbate the movement disorder. Benefit has been reported with the atypical antipsychotic clozapine (which must be used with caution because of the risk of agranulocytosis) but results with other atypical antipsychotics such as risperidone and olanzapine have been mixed; quetiapine appears to be reasonably well tolerated. Other drugs that have been tried include anticholinesterases such as donepezil and rivastigmine; ECT may be considered in patients refractory to drug treatment.[36,37]

Antipsychotics have been used for palliative treatment of agitation and restlessness in patients with **terminal restlessness**.[38-40] Although antipsychotics may exacerbate the existing tendency to myoclonus and convulsions in these patients and may not produce adequate sedation in the terminal phase, haloperidol can be used where sedation is not required. Some[38-40] even consider haloperidol to be the drug of choice; chlorpromazine[38-40] and olanzapine have been used as alternatives. Benzodiazepines (such as lorazepam or midazolam), levomepromazine, and propofol have also been used.[38,40]

Paraphilias and other **deviant sexual behaviour** are rare in women so treatment is focused largely towards men; it consists mainly of psychotherapy and the use of libido-suppressing drugs such as the anti-androgens.[41-44] The use of such pharmacotherapy is controversial and involves not only medical but legal issues. Drugs used for their anti-androgenic action include cyproterone and medroxyprogesterone. Gonadorelin analogues have also been tried for suppression of libido.[42] Medroxyprogesterone has also been used for the control of intrusive disinhibited sexual behaviour in elderly men with dementia. SSRIs may be used in less severe cases, especially in the control of fantasies associated with various paraphilias; they may also be used with an antihormonal drug if the latter provides inadequate improvement alone.[43,44] The antipsychotic benperidol is used in some countries for the management of sexual deviations but its value is not established. In general, few well-controlled blinded studies have been conducted into the pharmacological treatment of sexual offenders and there is no evidence that drug treatment reduces the rate of re-offending.

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Mania. Mania usually occurs as part of bipolar disorder. The treatment of acute attacks of mania including mention of the role of antipsychotics is described under Bipolar Disorder, p. 397.2.

Schizophrenia. Schizophrenia is a complex disorder associated with a high morbidity; it may be a group of related syndromes rather than a single disorder. Schizophrenia begins most commonly in late adolescence to the early twenties and many patients develop a chronic illness with repeated relapses. The estimated prevalence is between 0.2 to 1% in the general population. The main clinical features of acute schizophrenia syndrome can be divided into psychotic features such as delusions and hallucinations, and disorganised features involving speech, thought, and behaviour (together often known as 'positive' symptoms). The main features of the chronic syndrome are apathy, lack of drive, and social withdrawal (so-called 'negative' symptoms). Positive symptoms tend to respond better to drug therapy than negative symptoms. The pathophysiological mechanism of schizophrenia is unclear. Since classical antipsychotics used in the treatment of schizophrenia block dopamine D_2 receptors in the midbrain it has been suggested that dopaminergic system overactivity may be involved. However, the efficacy of atypical antipsychotics such as clozapine (see below), which is a relatively weak dopamine D_2 inhibitor, has raised the possibility that an imbalance of other neurotransmitters such as serotonin and adenosine may also be involved (see also Action, under Chlorpromazine, p. 1046.1).

The **treatment** of schizophrenia consists mainly of a combination of psychosocial therapy and antipsychotics.[1-16] Drug treatment must be started as soon as possible for best outcome. There is little difference in the efficacy of classical antipsychotics such as chlorpromazine and haloperidol. The atypical antipsychotic clozapine appears to be more effective than classical antipsychotics in the management of both positive and negative symptoms, but its use is restricted because it can cause potentially fatal agranulocytosis. Comparative studies have shown that other atypical antipsychotics are at least as effective on positive symptoms as the classical antipsychotics, although claims of greater effects on negative symptoms remain to be proven.

Choice of therapy depends on the risk of adverse effects (which vary between the different groups of antipsychotics), any past treatment, and, unfortunately, cost. The atypical antipsychotics may be better tolerated than classical antipsychotics and, in particular, extrapyramidal symptoms may be less frequent. However, classical antipsychotics are still widely used, since the diversity of their preparations (tablets, oral liquids, injections, and depot injections) and lower cost offer advantages over the atypicals. Because the atypical antipsychotics risperidone and olanzapine have been associated with an increased risk of stroke when used in elderly patients with dementia (see the Elderly, under Risperidone, p. 1105.1), some UK guidelines[17] have recommended that other antipsychotics should be considered for patients with a history of stroke, transient ischaemic attacks, or other cerebrovascular disease even in the absence of dementia. However, there is little evidence to guide prescribing in older patients.[18]

There is great interindividual variation in response to antipsychotics, and choosing the most appropriate one may require a trial of antipsychotics from different chemical groups and careful adjustment of dosage. The Royal College of Psychiatrists in the UK has issued advice for those considering the use of higher than normally recommended doses of antipsychotics (see under Administration in the Uses and Administration of Chlorpromazine, p. 1046.1).

However, in recent years there has been a trend in favour of lower doses of antipsychotics, often with adjunctive benzodiazepines (see below). The use of more than one antipsychotic at the same time is not usually recommended.

About 30% of patients may have little or no response to classical antipsychotics while many others have only a partial response. Such **resistant schizophrenia** may be due to poor patient compliance, which is a major problem in schizophrenic patients; lack of compliance may be a result of adverse effects (see below for possible treatments) or because the patient has a relapse while on medication and is unable to maintain treatment.[19] A patient should not be considered resistant to therapy until at least 2 different antipsychotics (NICE also recommends that at least one of these should have been an atypical[13]) have each been given for an adequate trial period (at least 6 to 8 weeks). If other drugs are still ineffective, clozapine may be tried; it should be given for at least 3 months before resorting to measures such as ECT or the use of adjunctive drugs (see below).

After the initial control of schizophrenia with antipsychotics, relapse rates are high in those who stop treatment, therefore **maintenance** therapy is probably warranted. Some recommend the use of lower doses of antipsychotics during maintenance to reduce adverse effects, although this may increase the risk of relapse. The decision to withdraw an antipsychotic completely in a stabilised patient is complex and depends on the number of previous psychotic episodes. In some cases maintenance therapy may need to be indefinite. Regular injections of long-acting depot antipsychotics are sometimes used for maintenance therapy especially if compliance is a problem.[13,20] They are particularly useful for patients living in the community, and may also be advantageous for those who respond poorly to therapy because of increased first-pass metabolism or intestinal malabsorption. Concern over the possibility of increased extrapyramidal effects and other adverse effects with depot antipsychotics has not been substantiated.

Adjunctive drugs have been used in schizophrenia either to augment antipsychotics or reduce their adverse effects.[21] The short-term addition of a *benzodiazepine* to the initial treatment of acute episodes of schizophrenia can provide a useful extra sedative and anxiolytic effect. It may also allow a smaller dose of antipsychotic to be used and thereby reduce the likelihood of extrapyramidal effects. However, a systematic review[22] concluded that the available evidence for such use is poor and inconclusive.

The use of *antimuscarinic antiparkinsonian drugs* for the treatment or prophylaxis of antipsychotic-induced extrapyramidal adverse effects is controversial (see Extrapyramidal Disorders on p. 1049.2). They are particularly effective in the management of acute dystonic reactions but efficacy in drug-induced parkinsonism itself may be minimal and little benefit has been found in akathisia. Fears that the long-term use of antimuscarinics increases the risk of tardive dyskinesia appear to be unfounded, although they may worsen the condition and should be stopped if it develops. However, the adverse effects of antimuscarinics can be troublesome and may compound the antimuscarinic actions of the antipsychotic. Antimuscarinics also have euphoric effects. Routine use of prophylactic antimuscarinics is therefore not indicated with the possible exception of short-term use in patients at high risk of developing dystonias, or in patients with a history of drug-induced dystonias. Antimuscarinics may be given on a short-term basis to treat dystonias.

Addition of *lithium* to antipsychotic treatment may be worthwhile in some patients who fail to respond to an antipsychotic alone, although there is the danger of an interaction (see p. 431.3).

The value of treatment of depressive symptoms of schizophrenia with *antidepressants* is not established but the addition of antidepressants such as the tricyclics is considered worth a trial for depression occurring during the recovery phase after an acute episode of psychosis.

Carbamazepine has produced modest benefit in some patients with refractory schizophrenia, the main effect being a reduction in accompanying symptoms such as excitement, impulsivity, and aggression, but use of carbamazepine with haloperidol has also resulted in reduced haloperidol concentrations and clinical deterioration in a few patients. A systematic review[23] found no significant benefit of adjunctive carbamazepine therapy. *Valproate* has also been tried; however, a systematic review[24] found no data to support or refute the use of valproate, either alone or in combination with antipsychotics, in the treatment of schizophrenia.

Propranolol in high doses has been reported to be beneficial in refractory schizophrenia but several controlled studies of adjunctive use have found slight or no benefit. However, it may be of use as an adjunct in patients who develop akathisia unresponsive to antimuscarinics.

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Sedation

Since sedatives reduce excitement and anxiety, they may be used before or during various medical procedures to alleviate fear and produce a state of calmness in the patient. A practical aim for situations requiring **conscious sedation**, for example in *dentistry* or during investigative procedures such as *endoscopy*, may be the reduction or abolition of physiological and psychological responses to the stress without loss of consciousness, cooperation, or protective reflexes. A greater degree of sedation may be required for patients in *intensive care* and some consider that patients should be maintained asleep but easily rousable. The difference between sedatives and hypnotics is mainly dose related. The same drug or group of drugs can have both effects, larger doses being necessary for a hypnotic effect, that is to produce a state of sleep.

Some specific situations where sedation may be required are discussed below. The use of sedatives in premedication for anaesthesia is discussed on p. 1899.1.

Dental sedation. Intravenous midazolam has largely superseded diazepam for sedation in dental procedures. However, midazolam needs to be given slowly in small increments as its sedative end-point is reached much more abruptly than with diazepam. Midazolam has a more rapid onset of action and recovery, and produces a greater degree of amnesia than diazepam, but it can cause hallucinations in children.[1] There is insufficient evidence to support the routine use of intravenous sedation for dental procedures in children under the age of 16 years and it is recommended that such use, along with the use of general anaesthetics, combination regimens, and non-standard routes, should be restricted to specialist centres or hospital settings.[2]

Inhaled nitrous oxide (usually 20 to 40% with oxygen[3]) is a widely used analgesic and sedative for conscious sedation of patients with mild to moderate anxiety about dental procedures.[3,4] It is relatively safe and simple to use although there is some concern over its long-term effect on dental staff.[3,4] Nitrous oxide inhalation is well tolerated by children and remains the preferred technique in the management of anxiety in such patients although a certain amount of patient cooperation is required[1,2,3] and supplementary local analgesia is recommended in potentially painful procedures.[2]

Oral sedatives may also be used to provide conscious sedation[4] and are particularly useful to ensure that the patient has a restful night before the procedure; hypnotics may be used for 1 to 3 nights before. Those drugs used include the benzodiazepines diazepam, nitrazepam, and temazepam; temazepam is preferred when it is important to minimise any residual effects. The antihistamines hydroxyzine and promethazine have been used in children.[1,4,5] Oral sedatives have no analgesic effects and appropriate analgesia should be given.[5] It has been suggested that the efficacy of the oral sedative in adult patients can be enhanced by the careful addition of inhaled nitrous oxide; the depth of sedation can be changed as necessary by varying the titration of the latter.[4]

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Endoscopy. The practice of giving sedation routinely before endoscopy varies widely between and within countries.[1-3] It is unclear whether sedation improves patient comfort and the ease of performing the procedure;[1] there may be a failure to distinguish between the need for sedation and the need for analgesia in such procedures. Ultimately the acceptability of unsedated endoscopy differs from patient to patient and procedure to procedure,[2] and it may be appropriate to offer patients the choice.[4]

Intravenous benzodiazepines are commonly used for sedation during endoscopy.[1,2,5,6] Midazolam is generally preferred to diazepam because of its shorter duration of action and greater amnestic effects.[6] Since hypoventilation and oxygen desaturation may occur with benzodiazepines and the procedure itself can lower oxygen saturation, some recommend the use of prophylactic nasal oxygen with oxygen saturation monitoring.[2,3,5,6]

Intravenous opioid analgesics such as morphine and pethidine have also been given but they have largely been replaced by the newer shorter-acting opioids, for example fentanyl, which have faster recovery times.[3,6] Benzodiazepines have often been given with opioids, including pethidine, since such combinations may reduce gagging and increase patient tolerance.[2] They can be used together to achieve deep sedation at higher doses than those used for conscious sedation. However, there is an increased risk of cardiorespiratory effects and, possibly, fatalities with such combinations.[2,5] Therefore, the use of the lowest effective doses has been recommended[3,5] and opioids should be given before benzodiazepines, where possible, and their effects monitored before proceeding.[5] The addition of intravenous diphenhydramine, droperidol (but see also Adverse Effects, Treatment, and Precautions of Droperidol, p. 1072.2), or promethazine to such combinations may result in deeper sedation and may be used in patients who are inadequately sedated.[6]

Low-dose intravenous propofol has also been used for conscious sedation as an alternative to, or with, midazolam and opioids.[4] It potentiates the effects of benzodiazepines and opioids, thus reducing the doses required for sedation and analgesia.[6] Propofol has been used alone for deep sedation especially in prolonged or complex procedures; benefit has not been shown conclusively for shorter procedures.[6] The risk of adverse effects may limit its use[6] and the presence of an anaesthetist is usually required.[5] Fospropofol, a prodrug of propofol, is available in some countries for sedation.

Continuous monitoring of the sedated patient's haemodynamic and ventilatory status, and level of consciousness is recommended.[2-10]

The use of topical anaesthetics such as lidocaine should probably be reserved for those who prefer to undergo endoscopy without sedation as topical anaesthesia appears to serve little useful function in patients premedicated with benzodiazepines or opioids.[4,11] There appears to be no practical difference between individual topical anaesthetics. Sprays are safer and may be more effective than lozenges,

but even when using a spray it is difficult to anaesthetise the oropharyngeal region effectively.

There is great variation in the methods of sedation and analgesia used for **children** undergoing endoscopy.[7-10] The choice between general anaesthesia and sedation in these patients is subject to debate.[7] Many of the regimens used appear to be similar to those used in adults; drugs commonly used include midazolam, opioids such as fentanyl or pethidine, and propofol.[7,10] However, the use of propofol is generally not recommended in children (see Incidence of Adverse Effects, under Propofol, p. 1913.3). In the UK, general anaesthesia is the favoured method for younger children; premedication with oral midazolam has also been used.[8]

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Intensive care. Not all patients in intensive care units require sedatives if sufficient analgesia is achieved, particularly after the first 24 to 48 hours, but most will require a balanced combination of analgesics and sedatives to relieve pain and anxiety.[1-9] It is inappropriate to use high doses of analgesics to achieve deep sedation and it is also inappropriate to use sedatives alone for patients who are in pain. Adequate analgesia is recommended before giving sedatives in order to avoid over-sedation.[4,7] The required level of sedation may vary but, in general, many consider patients should be maintained asleep but easily rousable.

Most sedatives and analgesics are given parenterally. Continuous intravenous infusion avoids the peaks and troughs of analgesia and sedation associated with intermittent intramuscular or intravenous dosage, but to what extent it improves patient outcomes is unclear: sedation produced in this way may prolong the need for mechanical ventilation and increase pulmonary complications.

Opioid analgesics have both sedative and analgesic properties and are appropriate for sedation when pain is anticipated, although special care is required in those not artificially ventilated. The antitussive action of the opioids may also help ventilated patients to tolerate a tracheal tube. The choice of opioid may vary between centres, as well as with patient characteristics. Morphine is a suitable opioid in many situations in intensive care[6] but has a slow onset of action. If prolonged sedation is required, analgesia can be obtained by a loading dose followed by a continuous infusion. Many centres now favour the use of one of the phenylpiperidine derivatives, fentanyl, alfentanil, sufentanil, or remifentanil.[5-9]

Propofol is widely used for short-term sedation (up to 72 hours) in intensive care units,[4-9] although concerns have been raised about its safety, particularly in children (in whom use is generally not recommended), or with prolonged use or higher rates of infusion (see also Incidence of Adverse Effects, under Propofol, p. 1913.3). It may be particularly useful in neurosurgical patients to reduce raised intracranial pressure,[4,8] or when rapid awakening is important.[6]

Benzodiazepines induce sleep and reduce anxiety and muscle tone as well as providing profound amnesia; however, they do not provide analgesia. Midazolam has a rapid onset and short duration of action following single doses, and has largely replaced diazepam as the benzodiazepine of choice for sedation. It is particularly favoured for longer-term sedation (more than 72 hours).[5,9] The half-life of midazolam can be substantially increased when given as a continuous intravenous infusion for long-term sedation in patients in intensive care. Lorazepam has also been used[1,6] particularly in the USA,[6] and may be associated with less variability in awakening times, although onset of action may be slower than midazolam.

All benzodiazepines tend to produce cardiovascular and respiratory depression and care is required if they are used with opioids as is usually the case in this setting.

Flumazenil is a specific benzodiazepine antagonist and some suggest that it may be of use to assist the return of spontaneous respiration and consciousness in patients receiving benzodiazepines. Multiple doses may be required as it has a short duration of action.[1] However, its routine use after prolonged benzodiazepine treatment is not usually recommended because of the risk of inducing withdrawal symptoms.[6]

Dexmedetomidine is also approved for use in intensive care as a sedative; it is stated to have analgesic-sparing properties.[6]

Ketamine has been investigated for sedation in the intensive care setting[4] and appears to be effective; it may be used as an adjuvant.[8,9] Clonidine is also used as an adjuvant to other drugs.[3,6,8,9] In agitated or delirious patients haloperidol may be used.[4,6]

Stopping treatment with sedatives such as benzodiazepines, opioids, and propofol too rapidly may lead to withdrawal symptoms,[4,7] especially after high doses or prolonged sedation (more than 1 week). Doses should be tapered to prevent such symptoms. Tolerance to benzodiazepines can develop and may be related to long-term sedation (2 days or more); tolerance to opioids has also been reported.[7]

Methods of sedation and analgesia for **children** in intensive care are subject to debate. Many of the regimens used appear to be similar to those used in adults or modifications of existing regimens for paediatric sedation. Drugs commonly used include midazolam and opioids such as fentanyl or, in particular, morphine.[3] However, there has been some concern over a report of encephalopathy associated with the prolonged use of midazolam with fentanyl for sedation in infants under intensive care (see Encephalopathy, under Effects on the Nervous System, p. 1066.2). As mentioned above, propofol is not recommended for children in intensive care.

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Sleep disorders

The exact function of sleep is uncertain but it is believed to be involved in energy conservation, total body restoration and recuperation, and development and growth. There are two states of sleep: non-rapid-eye-movement (non-REM) sleep, which is subdivided into 4 stages, and rapid-eye-movement (REM) sleep, sometimes called stage 5. Initially there is a period of light sleep (stages 1 and 2) followed by deep sleep (stages 3 and 4); this latter period is also known as slow-wave sleep. After stage 4, which occurs about 90 minutes after first falling asleep, there is a period of REM sleep (stage 5) during which most dreams occur and EEG traces show high-frequency waves. During a period of sleep there are several cycles of stages 1 to 4 followed by REM sleep, with periods of non-REM sleep becoming shorter and periods of REM sleep longer. It is the slow-wave sleep that is considered to be the more restorative. Most healthy adults sleep for single periods of between 7 to 8 hours a day, although there is a wide range of normal sleeping time (from 4 to 11 hours). In old age there is less slow-wave sleep and sleep becomes more fragmented.

Sleep disorders include insomnia (see below), hypersomnia such as narcolepsy, p. 2314.3, in which the timing, length, and quality of sleep is altered, and the parasomnias (see Sleep-associated Movement Disorders, p. 1034.2) in which abnormal events occur during sleep.

Insomnia. Insomnia is the inability to achieve or maintain sleep and is the most common of the sleep disorders.[1-20] It often leaves sufferers feeling unrefreshed by sleep and may lead to impaired daytime performance.

- Transient insomnia may occur in those who normally sleep well and may be due to an alteration in the conditions that surround sleep, for example noise, or to an unusual pattern of rest as in shift work or travelling between time zones (jet lag). It may also be associated with acute disorders.
- Short-term insomnia is often related to an emotional problem or more serious medical illness such as acute pain. It may last for a few weeks and may recur.
- Chronic insomnia may be attributed to an underlying psychiatric disorder, especially depression or anxiety, to alcohol or drug abuse, to certain drug treatments, to excessive caffeine intake, to daytime napping, or to physical causes such as pain, pruritus, or dyspnoea.

Management of insomnia requires resolution of any stressful precipitant or identification and treatment of any underlying causes, with an emphasis on non-pharmacological measures such as counselling, behavioural therapy, development of relaxation techniques, and avoidance of stimulant substances. Hypnotic drugs should ideally be reserved for short courses in the acutely distressed patient; they should be avoided in the elderly, and their use is rarely justified in children. Generally, hypnotics should be given at the lowest effective dose for as short a period as possible. In transient insomnia one or two doses of a short-acting hypnotic may be indicated, whereas in short-term insomnia intermittent doses of a short-acting hypnotic given for no more than 3 weeks (preferably only 1 week) may be appropriate. Chronic insomnia rarely benefits from hypnotics and routine use of hypnotics is undesirable. Tolerance can develop rapidly (in 3 to 14 days with continuous use) and withdrawal after long-term use can lead to rebound insomnia and a withdrawal syndrome.

Benzodiazepines are generally regarded as the hypnotics of choice. They hasten sleep onset, decrease nocturnal awakenings, increase total sleeping time, and often impart a sense of deep and refreshing sleep. Slow-wave sleep and REM sleep are, however, reduced and the extra sleeping time is largely made up of relatively light sleep. A short-acting benzodiazepine such as temazepam is generally used when residual sedation is undesirable, if falling asleep is a problem, or, when necessary, in elderly patients. However, a withdrawal syndrome is more common with the short-acting benzodiazepines. Longer-acting benzodiazepines such as nitrazepam are indicated when early waking is a problem and possibly when an anxiolytic effect is needed during the day or when some impairment of psychomotor function is acceptable.

Because of the hazard of dependence with benzodiazepines (see p. 1065.1), the UK CSM[21] has issued certain recommendations:

- they should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress
- they should be given in the lowest dose which controls symptoms (if possible, intermittently)
- they should not be continued beyond 4 weeks
- they should be withdrawn by gradual tapering of the dose to zero

Subsequently, the EU Committee on Proprietary Medicinal Products (CPMP) has recommended that the treatment period should be limited to 2 weeks when brotizolam, midazolam, or triazolam are used.[22]

Tolerance to the hypnotic effects of benzodiazepines develops rapidly, with sleep latency and pattern returning to pretreatment levels within a few weeks of starting treatment.

Several other drugs have been used as alternatives to the benzodiazepines. Zaleplon, zopiclone, and zolpidem act on the same receptors or receptor subtypes as the benzodiazepines although structurally they are unrelated. Their short duration of action makes them more suitable for patients who have trouble falling asleep. The CPMP has recommended that treatment with zolpidem should be limited to a maximum of 4 weeks.[22] It remains to be proven whether these drugs offer any advantages over the benzodiazepines. Indeed, the CSM considers that zopiclone has the same potential for adverse psychiatric reactions, including dependence, as benzodiazepines.[23] NICE[24] in the UK found no compelling evidence of any clinically useful differences between these drugs and the shorter-acting benzodiazepines in terms of efficacy, adverse effects, or potential for dependence or abuse, and recommends that patients who do not respond to zaleplon, zopiclone, zolpidem, or benzodiazepines should not be switched between these hypnotics; patients may be switched if adverse effects directly related to a specific drug occur.

The tricyclic antidepressant, doxepin, may be used in the management of insomnia characterised by difficulty in sleep maintenance.[25] It is given in lower doses than those used for depression.

The use of cloral hydrate and its derivatives as hypnotics is now very limited. They have been used as alternatives to benzodiazepines in the elderly, although there is no convincing evidence of any special value in these patients. They used to be considered useful hypnotics for children but such use is rarely justified.

Clomethiazole has also been used as an alternative to benzodiazepines in the elderly. Nasal and conjunctival

irritation may be troublesome, and the danger of overdosage and risk of dependence should be considered.

Some antihistamines have hypnotic properties and a number, including alimemazine, diphenhydramine, doxylamine, and promethazine, are marketed for insomnia. They may cause troublesome antimuscarinic effects and those with longer half-lives may cause hangover effects. Promethazine is also popular for use in children, but such use is not usually justified (see Sudden Infant Death Syndrome under Adverse Effects of Promethazine, p. 639.1, for further details).

Barbiturates are no longer recommended as hypnotics because of their adverse effects. The CSM[26] has advised that barbiturates should only be used for insomnia that is severe and intractable when there are compelling reasons to, and then only in patients already taking barbiturates. It was also advised that attempts should be made to wean patients off barbiturate hypnotics. Similarly, compounds such as ethchlorvynol, and methaqualone are not recommended.

Alcohol is not recommended because it has a short weak hypnotic action, and rebound excitation can result in early morning insomnia. Its diuretic effects can interrupt sleep and chronic use can lead to rapid development of tolerance and addiction.

Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity in the treatment of insomnia. Its efficacy is difficult to substantiate and, since the publication of reports linking tryptophan with the eosinophilic-myalgia syndrome, preparations indicated for insomnia have been withdrawn from the market in many countries.

Melatonin, a hormone believed to be involved in the maintenance of circadian rhythms, may be useful in the treatment of insomnias such as those due to jet lag[27] or other disorders (where it might act by resetting the body clock), and in the elderly. However, its benefits have been questioned,[28] and certainly evidence for a direct hypnotic effect is less conclusive; its sleep-inducing properties are usually only seen after very high, supraphysiological concentrations have been attained.[5,6] Ramelteon, a melatonin receptor agonist, is used as a hypnotic in some countries.

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Sleep-associated movement disorders. Parasomnias are motor disorders, with or without autonomic features, that occur during sleep or are exaggerated by sleep. Some of the main parasomnias include nightmares, night terrors, sleepwalking (somnambulism), nocturnal enuresis (p. 2349.1), bruxism (teeth grinding), head banging, and aggression during sleep. Other common movement disorders associated with sleep are restless legs syndrome and periodic limb movements in sleep. Parasomnias are common but rarely require treatment with drugs other than the symptomatic treatment of sleep-related medical problems. The management of some of these conditions is discussed briefly below.

The **restless legs syndrome** is characterised by an unpleasant creeping sensation deep in the legs with an irresistible urge to move them. Symptoms begin during relaxation in the evenings and in bed, and interfere with the ability to fall asleep. The aetiology of this condition is obscure and treatment has been largely empirical.[1-11] Drug treatment may not always be necessary and non-pharmacological methods such as good sleep hygiene should be tried initially.[1,3,7,8,12] There have been reports of efficacy with a wide range of treatments, although few have been well studied. Dopaminergic therapy has emerged as a common first-line treatment, a long-acting agonist, such as cabergoline, pergolide, pramipexole, or ropinirole, being preferred in order to avoid the complications associated with levodopa.[5,6,8-12] Anticonvulsants, such as carbamazepine, clonazepam, and gabapentin may be of use in those intolerant of dopamine agonists or in those who require additional medication.[5,8-11] Other drugs that have been reported to be of benefit include some opioids, clonidine, and the benzodiazepines.[5,7-12] Iron supplementation may be effective if the syndrome is associated with iron deficiency.[2-4,7-12] Many patients with restless legs syndrome exhibit **periodic limb movements in sleep**,[2,3] characterised by repetitive periodic leg and foot jerking during sleep. Treatments tried are similar to those for the restless legs syndrome; clonazepam and levodopa are amongst the drugs shown to be of benefit.

Some **parasomnias** have responded to treatment with benzodiazepines.[13-15] These include bruxism, head banging, aggression during sleep, night terrors, and sleepwalking.

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Acamprosate Calcium

(BANM, USAN, rINNM)

Acamprosat-Calcium; Acamprosate calcique; Acamprosate de Calcium; Acamprosato de calcio; Acamprosatum calcicum; Akamprosaattikalsium; Akamprosát vápenatá sůl; Akamprosatkalcium; Akamprosato kalcio druska; Akamprozát-kalcium; Calcii Acamprosatum; Calcium Acetylhomotaurinate; Кальций Акампрозат.

Calcium 3-acetamido-1-propanesulphate.

$C_{10}H_{20}CaN_2O_8S_2$=400.5

CAS — 77337-76-9 (acamprosate); 77337-73-6 (acamprosate calcium).

ATC — N07BB03.

UNII — 59375N1D0U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Acamprosate Calcium). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 5.5 to 7.0.

Uses and Administration

Acamprosate has a chemical structure similar to that of the endogenous amino acid, homotaurine, which is a structural analogue of gamma-aminobutyric acid (GABA—p. 2509.2) and taurine (p. 2626.2). It is given as the calcium salt to prevent relapse in alcoholics who have been weaned off alcohol (below). The usual oral dose is 666 mg of acamprosate calcium given three times daily. In patients weighing less than 60 kg a suitable dose is 666 mg at breakfast followed by 333 mg at midday and 333 mg at night. For doses in patients with renal impairment, see below. Treatment should be started as soon as possible after alcohol withdrawal and maintained, even if the patient relapses, for the recommended period of 1 year.

Administration in renal impairment. It is considered likely that accumulation of acamprosate would occur with prolonged use of therapeutic doses in patients with renal impairment. It has been reported that the mean maximum concentration of acamprosate after a single 666-mg oral dose was 813 nanograms/mL in 12 patients with moderate or severe renal impairment compared with 198 nanograms/mL in 6 healthy subjects; values for the plasma elimination half-life were 47 and 18 hours, respectively.

Licensed product information in the UK contra-indicates the use of acamprosate in patients with renal impairment (serum creatinine greater than 120 micromoles/litre). US licensed product information also contra-indicates the use of acamprosate in those with severe renal impairment (creatinine clearance (CC) less than 30 mL/minute). However, in those with moderate impairment (CC 30 to 50 mL/minute), an initial oral dose of 333 mg three times daily may be given.

1. Wilde MI, Wagstaff AJ. Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 1997; 53: 1038–53.

Alcohol dependence. Acamprosate is considered to be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p. 1735.1). A systematic review[1] of 24 randomised, placebo-controlled studies involving 6915 patients concluded that acamprosate helps to prevent relapse and increase the number of drink-free days during treatment and possibly for up to one year thereafter. However, other outcomes such as preventing a return to heavy drinking were not statistically significant with acamprosate treatment; in addition, its use with naltrexone did not produce any additional benefit.

Several mechanisms have been proposed to account for acamprosate's action including inhibition of neuronal hyperexcitability by antagonising excitatory amino acids such as glutamate.

1. Rösner S, *et al.* Acamprosate for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2010 (accessed 01/02/11).

Gambling. A case report of a patient who noticed that she was able to avoid excessive gambling while receiving treatment with acamprosate for alcoholism.[1]

1. Raj YP. Gambling on acamprosate: a case report. *J Clin Psychiatry* 2010; 71: 1245–6.

Tinnitus. Acamprosate has been tried[1] in the management of tinnitus (p. 1994.1) with some beneficial results.

1. Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: double-blind study. *Braz J Otorhinolaryngol* 2005; 71: 618–23.

Adverse Effects

The main adverse effect of acamprosate is dose-related diarrhoea; nausea, vomiting, and abdominal pain occur less frequently. Other adverse effects have included pruritus, and occasionally a maculopapular rash; bullous skin reactions have occurred rarely. Depression and fluctuations in libido have also been reported. Hypersensitivity reactions including urticaria, angioedema, and anaphylaxis have been reported very rarely.

Effects on the skin. A case of erythema multiforme in a woman with cirrhosis of the liver has been attributed to use of acamprosate[1] although both the diagnosis and any association with acamprosate have been seriously challenged.[2]

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Precautions

Acamprosate is not metabolised via the liver and its pharmacokinetics are not altered in patients with mild to moderate hepatic impairment (Child-Pugh Classes A and B); no change in dose is required in such patients. In patients with severe hepatic impairment (Child-Pugh Class C), UK licensed product information contra-indicates the

use of acamprosate although no advice is provided in US licensed information. For precautions regarding the use of acamprosate in patients with renal impairment, see under Uses and Administration, p. 1034.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acamprosate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/07/11)

Pharmacokinetics

Absorption of acamprosate from the gastrointestinal tract is slow but sustained and is subject to considerable interindividual variation. Steady-state concentrations occur after dosage for 7 days. Bioavailability is reduced if given with food. Acamprosate is not protein bound and although it is hydrophilic it is reported to cross the blood-brain barrier. Acamprosate does not appear to be metabolised and is excreted unchanged in the urine. The elimination half-life after oral doses has been reported to be about 33 hours.

References.

1. Saivin S, *et al.* Clinical pharmacokinetics of acamprosate. *Clin Pharmacokinet* 1998; 35: 331–45.
2. Xu F, *et al.* Pharmacokinetics of acamprosate calcium in healthy Chinese subjects after oral administration of three dosage levels. *Arzneimittelforschung* 2009; 59: 631–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Campral; *Austral.*: Campral; *Austria*: Campral; *Belg.*: Campral; *Canad.*: Campral; *Chile*: Campral; *Cz.*: Campral; *Denm.*: Campral; *Fr.*: Aotal; *Ger.*: Campral; *Hung.*: Campral†; *India*: Acamprol; *Irl.*: Campral; *Jpn*: Regtect; *Mex.*: Campral†; *Neth.*: Campral; *Norw.*: Campral; *Pol.*: Campral; *Port.*: Campral; *S.Afr.*: Besobrial; *Singapore*: Campral; *Spain*: Campral; Zulex†; *Swed.*: Campral; *Switz.*: Campral; *Turk.*: Campral; *UK*: Campral; *USA*: Campral.

Acecarbromal *(rINN)*

Acécarbromal; Acecarbromalum; Acetcarbromal; Acetylcarbromal; Ацекарбромал.

N-Acetyl-*N*'-(2-bromo-2-ethylbutyryl)urea.

$C_9H_{15}BrN_2O_3$=279.1

CAS — 77-66-7.

UNII — E47C56IGOY.

Profile

Acecarbromal is a bromureide with similar actions to those of carbromal (p. 1044.1). It has been used for its sedative properties but the use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Afrodor†; *Rus.*: Afrodor (Афродор)†.

Acepromazine *(BAN, rINN)*

Acepromazin; Acepromazina; Acépromazine; Acepromazinum; Asepromatsiini; Ацепромазин.

10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

$C_{19}H_{22}N_2OS$=326.5

CAS — 61-00-7.

ATC — N05AA04.

ATC Vet — QN05AA04.

UNII — 54EJ303F0R.

Acepromazine Maleate *(BANM, USAN, rINNM)*

Acepromazina, maleato de; Acépromazine, Maléate d'; Acepromazini Maleas; Acetylpromazine Maleate; Asepromazin Maleat; Maleato de acepromazina; Ацепромазина Малеат.

10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone hydrogen maleate.

$C_{19}H_{22}N_2OS.C_4H_4O_4$=442.5

CAS — 3598-37-6.

ATC — N05AA04.

ATC Vet — QN05AA04.

UNII — 37862HP2OM.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet).*

BP(Vet) 2014: (Acepromazine Maleate). A yellow crystalline powder. Soluble in water and in alcohol; freely soluble in chloroform; slightly soluble in ether. A 1% solution in water has a pH of 4.0 to 4.5.

USP 36: (Acepromazine Maleate). pH of a 1% solution is between 4.0 and 5.5. Protect from light.

Profile

Acepromazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has been given orally as the maleate in the treatment of anxiety disorders, hiccups, and nausea and vomiting. Doses equivalent to 10 to 20 mg of the base may be given as a single dose or up to three times daily for anxiety disorders; lower doses have been given for hiccups, and nausea and vomiting.

Acepromazine, as the base, has also been given in preparations for the management of insomnia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Plegicil; *Turk.*: Plegicil.

Multi-ingredient Preparations. *Fr.*: Noctran†.

Acepromethazine *(rINN)*

16-64 CB; Acepromethazina; Acéprométazine; Acepromethazinum; Ацепрометазин.

10-(2-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

$C_{19}H_{22}N_2OS$=326.5

CAS — 13461-01-3.

UNII — 984N9YTM4Y.

Profile

Acepromethazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It is available usually as the maleate in preparations for the management of insomnia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Mepronizine†; Noctran†.

Allobarbital *(USAN, rINN)*

Allobarbitaali; Allobarbitalum; Allobarbitone; Alobarbital; Diallylbarbitone; Diallylbarbituric Acid; Diallylmalonylurea; Diallymalum; NSC-9324; Аллобарбитал.

5,5-Diallylbarbituric acid.

$C_{10}H_{12}N_2O_3$=208.2

CAS — 52-43-7.

ATC — N05CA21.

ATC Vet — QN05CA21.

UNII — 8NT43GG2HA.

Profile

Allobarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used in combination preparations for the treatment of sleep disorders and pain but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Demalgonil†; *Pol.*: Krople Zoladkowe†; Pabialgin P†; *Turk.*: Spasmo-Panalgine.

Alprazolam *(BAN, USAN, rINN)*

Alpratsolaami; Alprazolám; Alprazolamas; Alprazolamum; U-31889; Алпразолам.

8-Chloro-1-methyl-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine.

$C_{17}H_{13}ClN_4$=308.8

CAS — 28981-97-7 (alprazolam).

ATC — N05BA12.

ATC Vet — QN05BA12.

UNII — YUS5MQ3IZY.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of alprazolam:

Bars; Benzo; Coffins; Dogbones; Fo' Bars; Fo's; Footballs; Forgetful Pills; Four Bars; French Fries; Gold Bars; Green Bars; Quad bar; School Buses; Sticks; Totem Poles; White Bars; X-Boxes; Xan-Bars; Xannies; Xanny; Xany Bars; Zanny; Zan-Bars; Zannies; Zanny-Bars; Zany bar; Zbars; Z-Bars.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Alprazolam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Alprazolam). A white to off-white crystalline powder. Insoluble in water; soluble in alcohol; sparingly soluble in acetone; freely soluble in chloroform; slightly soluble in ethyl acetate.

Uses and Administration

Alprazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term treatment of anxiety disorders (below) in oral doses of 250 to 500 micrograms three times daily, increased where necessary every 3 to 4 days to a total daily dose of 3 or 4 mg.

In the treatment of panic disorder, with or without agoraphobia, initial oral doses of 500 micrograms may be given three times daily, increased where necessary in steps of no more than 1 mg every 3 to 4 days; doses of up to 10 mg daily have been used.

In elderly or debilitated patients, an initial dose of 250 micrograms two or three times daily has been suggested. For doses in patients with hepatic or renal impairment, see below.

A modified-release preparation of alprazolam is also available for once-daily dosing.

Reviews.

1. Verster JC, Volkerts ER. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. *CNS Drug Rev* 2004; 10: 45–76.

Administration in hepatic or renal impairment. UK licensed product information advises caution when using alprazolam in patients with hepatic or renal impairment; it is contra-indicated in those with severe hepatic impairment. In the USA, licensed product information states that patients with advanced liver disease may be given an initial oral dose of 250 micrograms two or three times daily.

Anxiety disorders. Alprazolam has been tried in the management of anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1).

References.

1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; 160: 191–202.
2. Lepola UM, *et al.* Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; 8: 115–18.
3. Pollack MH, *et al.* Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol* 1993; 13: 257–63.
4. Spiegel DA. Efficacy studies of alprazolam in panic disorder. *Psychopharmacol Bull* 1998; 34: 191–5.
5. Rickels K. Alprazolam extended-release in panic disorder. *Expert Opin Pharmacother* 2004; 5: 1599–1611.
6. Uhlenhuth EH, *et al.* Cognitive style, alprazolam plasma levels, and treatment response in panic disorder. *Depress Anxiety* 2008; 25: E18–E26.

Depression. Although they may be useful for associated anxiety, benzodiazepines are not usually considered appropriate for treatment of depression (p. 398.1); however, some drugs such as alprazolam have been tried for this indication.[1]

1. Kravitz HM, *et al.* Alprazolam and depression: a review of risks and benefits. *J Clin Psychiatry* 1993; 54: (suppl): 78–84.

Premenstrual syndrome. Alprazolam has been reported[1-3] to produce a marginal to good response in the premenstrual syndrome (p. 2272.3) but others have not found it to be of benefit,[4] and the role of benzodiazepines is limited by their adverse effects. If benzodiazepines are selected it is recommended that in order to reduce the risk of dependence and withdrawal symptoms they should be carefully restricted to the luteal phase in selected patients.[5] Withdrawal symptoms may be more severe after short-acting drugs such as alprazolam. Antidepressant drugs such as SSRIs may be preferred.

1. Smith S, *et al.* Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol* 1987; 70: 37–43.
2. Harrison WM, *et al.* Treatment of premenstrual dysphoria with alprazolam: a controlled study. *Arch Gen Psychiatry* 1990; 47: 270–5.
3. Freeman EW, *et al.* A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995; 274: 51–7.
4. Evans SM, *et al.* Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. *Neuropsychopharmacology* 1998; 19: 499–516.
5. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. *Drug Safety* 1994; 10: 160–9.

Tinnitus. Alprazolam has been tried[1-4] in the management of tinnitus (p. 1994.1) although adverse effects can limit usefulness.

1. Johnson RM, *et al.* Use of alprazolam for relief of tinnitus: a double-blind study. *Arch Otolaryngol Head Neck Surg* 1993; **119:** 842–5.
2. Huynh L, Fields S. Alprazolam for tinnitus. *Ann Pharmacother* 1995; **29:** 311–12.
3. Vernon JA, Meikle MB. Masking devices and alprazolam treatment for tinnitus. *Otolaryngol Clin North Am* 2003; **36:** 307–20.
4. Jalali MM, *et al.* The effects of alprazolam on tinnitus: a cross-over randomized clinical trial. *Med Sci Monit* 2009; **15:** PI55–PI60.

Dependence and Withdrawal

As for Diazepam, p. 1065.1. Dependence may be a particular problem at the high doses used in the treatment of panic disorder.

For the purpose of withdrawal regimens, 250 micrograms of alprazolam may be considered equivalent to about 5 mg of diazepam.

Withdrawal symptoms. Nonconvulsive status epilepticus was reported[1] in a 64-year-old man with renal insufficiency who had stopped taking alprazolam 1 mg nightly after having taken it for several years; the authors noted that this symptom has also been reported with the withdrawal of diazepam and lorazepam.

1. Olnes MJ, *et al.* Nonconvulsive status epilepticus resulting from benzodiazepine withdrawal. *Ann Intern Med* 2003; **139:** 956–8.

Adverse Effects and Treatment

As for Diazepam, p. 1065.3.

Effects on the liver. A patient receiving phenelzine for depression developed abnormal liver enzyme values on 2 occasions when alprazolam was added to the treatment.[1] It was not possible to say if this was due to alprazolam alone or a synergistic effect with phenelzine.

1. Roy-Byrne P, *et al.* Alprazolam-related hepatotoxicity. *Lancet* 1983; **ii:** 786–7.

Effects on the skin. There have been some reports of alprazolam-induced photosensitivity.[1,2]

1. Kanwar AJ, *et al.* Photosensitivity due to alprazolam. *Dermatologica* 1990; **181:** 75.
2. Watanabe Y, *et al.* Photosensitivity due to alprazolam with positive oral photochallenge test after 17 days administration. *J Am Acad Dermatol* 1999; **40:** 832–3.

Overdosage. A retrospective analysis[1] of 2063 hospital admissions for benzodiazepine overdosage in one region of Australia between January 1987 and October 2002 found that patients who took an overdose of alprazolam were about twice as likely to require admission to intensive care as those taking other benzodiazepines. Flumazenil was required in 14% of the 131 alprazolam overdoses, and ventilation in 16%, which was also significantly more than for other benzodiazepines. Given the apparently greater toxicity of alprazolam in overdosage, its increasing prescription to groups at risk of self-poisoning was of concern.

1. Isbister GK, *et al.* Alprazolam is relatively more toxic than other benzodiazepines in overdose. *Br J Clin Pharmacol* 2004; **58:** 88–95.

Precautions

As for Diazepam, p. 1066.3.

Abuse. High doses of alprazolam taken after maintenance doses of methadone produced a 'high' without pronounced sedation; the drug was also misused by nonopioid-drug abusers.[1] The usual urine toxicology screens for benzodiazepines often give false-negative results for alprazolam because of the extremely low concentrations of metabolites excreted, making abuse difficult to detect. A subsequent review[2] considered that the literature did not support the widely held belief that alprazolam had a greater liability for abuse than other benzodiazepines, but the possibility could not be discounted.

1. Weddington WW, Carney AC. Alprazolam abuse during methadone maintenance therapy. *JAMA* 1987; **257:** 3363.
2. Rush CR, *et al.* Abuse liability of alprazolam relative to other commonly used benzodiazepines: a review. *Neurosci Biobehav Rev* 1993; **17:** 277–85.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of alprazolam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

From a study[2] of the distribution of alprazolam into breast milk in 8 women it was estimated that the average daily dose of alprazolam ingested by a breast-fed infant would range from 0.3 to 5 micrograms/kg or about 3% of a maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Oo CY, *et al.* Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk. *Br J Clin Pharmacol* 1995; **40:** 231–6.

Handling. Care should be taken to prevent inhaling particles of alprazolam and exposing the skin to it.

Hepatic impairment. Oral alprazolam 1 mg was absorbed more slowly in 17 patients with alcoholic cirrhosis with no ascites than in 17 healthy subjects.[1] Mean peak alprazolam concentrations occurred after 3.34 hours in the cirrhotic patients and 1.47 hours in the healthy subjects. Mean elimination half-life for cirrhotic patients was 19.7 hours compared with 11.4 hours for healthy subjects. However, there were no significant differences in the maximum plasma concentrations achieved. The results indicate that alprazolam, in common with other benzodiazepines that undergo oxidative metabolism, would accumulate to a greater extent in patients with alcoholic liver disease than in healthy subjects; the daily dose of alprazolam may need to be reduced by half in this population. See also Administration in Hepatic or Renal Impairment, p. 1035.3.

1. Juhl RP, *et al.* Alprazolam pharmacokinetics in alcoholic liver disease. *J Clin Pharmacol* 1984; **24:** 113–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alprazolam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Alprazolam is well absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations occurring within 1 to 2 hours of a dose. The mean plasma half-life is 11 to 15 hours. Alprazolam is 70 to 80% bound to plasma proteins, mainly albumin. It is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4. Metabolites include α-hydroxyalprazolam, which is reported to be about half as active as the parent compound, 4-hydroxyalprazolam, and an inactive benzophenone. Plasma concentrations of metabolites are very low. Alprazolam is excreted in the urine as unchanged drug and metabolites.

References.

1. Greenblan DJ, Wright CE. Clinical pharmacokinetics of alprazolam: therapeutic implications. *Clin Pharmacokinet* 1993; **24:** 453–71.
2. Wright CE, *et al.* Pharmacokinetics and psychomotor performance of alprazolam: concentration-effect relationship. *J Clin Pharmacol* 1997; **37:** 321–9.
3. Kaplan GB, *et al.* Single-dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. *J Clin Pharmacol* 1998; **38:** 14–21.
4. Park J-Y, *et al.* Effect of CYP3A5*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. *Clin Pharmacol Ther* 2006; **79:** 590–9.
5. Glue P, *et al.* Pharmacokinetics of an extended release formulation of alprazolam (Xanax XR) in healthy normal adolescent and adult volunteers. *Am J Ther* 2006; **13:** 418–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alplax; Alprazol; Amziax; Ansielix; Aplacaina†; Bayzolam; Becede; Bestrol; Calmol; Droxol; Emeral; Isoproxal; Krama; Medronal†; Nivelan N; Novazolam; Pirval; Plasedan†; Prenadona†; Prinox; Psicosedol†; PTA; Razolam; Relaxten; Rilow; Rospaz; Silarten†; Tensium; Thiprasolan; Tranquinal; Xanax; ***Austral.***: Alprax; Kalma; Ralozam; Xanax; ***Austria***: Alprastad; Xanor; ***Belg.***: Alpraz; Alprazomed; Docalprazo†; Topazolam†; Xanax; ***Braz.***: Alfron; Altrox; Apraz; Constante; Frontal; Neozolam; Teufron; Tranquinal; Zoldac; ***Canad.***: Apo-Alpraz; Novo-Alprazol†; Nu-Alpraz; Xanax; ***Chile***: Adax; Grifoalpram†; Prazam; Sanerva; Tricalma; Zotran; ***Cz.***: Frontin; Helex; Neurol; Xanax; ***Denm.***: Alprox; Tafil; ***Fin.***: Alprox; Xanor; ***Fr.***: Xanax; ***Ger.***: Cassadan†; Tafil; ***Gr.***: Antanax; Saturnil; Xanax; ***Hong Kong***: Alprax; Kalma†; Nalion†; Renax†; Xanax; ***Hung.***: Frontin; Helex; Xanax; ***India***: Alap; Aleez; Alep; Alltop; Alp; Alpam; Alparazole; Alpkair; Alpose; Alpra; Alpradol-MD; Alpraquil; Alprax; Alprocontin†; Alprose; Alprosym; Alrif; Alzex; Alzoact; Alzocum; Alzokam; Alzolam; Alzomax; Alzopax; Alzot; Alzy; Anax; Anxicalm; Anxico; Anxit; Anxorel; Anxyl; Anzal; Anzi; Anzilum; Atam; Ateez; Atrest; Balmusa; Berest; Besquil; Bio Zolam; Bliz MD; Calmtec; Dalp; Eurelax; Eurolam; FAD; Pinezol; Hiprazole; Indolam; Jolistar; Kaprolam; L-Peez; Lamcin; Loral; Luzam; Manorest; Morecalm; Nitril; Norex; Notence; Onapract; Pacyl; Restyl; Tranax; Xycalm; Zolam; ***Indon.***: Actazolam; Alganax; Alviz; Apazol; Atarax; Calmlet†; Feprax; Prixitas; Grazolam; Soxietas†; Xanax; Zolastin; Zypraz; ***Irl.***: Alprol; Alprox†; Calmax; Gerax; Xanax; ***Israel***: Alpralid; Alprox; Xanagis; Xanax; ***Ital.***: Alpravecs; Alprazig; Frontal; Mialin; Valeans; Xanax; ***Malaysia***: Alpraline; Alpranax; Apo-Alpraz; Asolan; Besquil; Prazovex; Xanax; ***Mex.***: Alzam; Farmapram; Irizz; Neupax; Noxeprom; Pisalpra; Tafil; Tazun; ***Neth.***: Xanax; ***Norw.***: Xanor; ***NZ***: Xanax; ***Philipp.***: Altrox; Xanor; ***Pol.***: Afobam; Alprazomerck; Alprox; Neurol; Xanax; Zomiren; ***Port.***: Pazolam; Prazam; Unilan; Xanax; ***Rus.***: Alzolam (Алзолам); Helex (Хелекс); Neurol (Неурол); Xanax (Ксанакс); Zolomaks (Золомакс); ***S.Afr.***: Adco-Alzam; Azor; Xanor; Zopax; ***Singapore***: Alzolam; Apo-Alpraz; Dizolam; Xanax; Zacetin; ***Spain***: Trankimazin; ***Swed.***: Xanor; ***Switz.***: Xanax; ***Thai.***: Alcelam; Allam; Alnax; Alpazam; Alpralan; Alpramed; Alprax†; Anax†; Anpress; Dizolam†; Farzolam; Inzolam; Manex†; Marzolam; Mitranax; Moxinax; Pharnax; Prazol; Siampraxol; Sunax; Xalam; Xanadine; Xanax; Xiemed; Zolam; ***Turk.***: Xanax; ***UK***: Xanax; ***USA***: Niravam; Xanax; ***Venez.***: Abaxon; Alpram; Ansilan; Tafil.

Multi-ingredient Preparations. ***Arg.***: Alplax Digest; Alplax Net; Ansielix Digest; Euciton Stress; Sidomal; Tensium Gastric; Tranquinal Soma; ***India***: Alamflu; Alltop-P; Alltop-S; Alp-FT; Alp-FTD; Alprax Forte; Alprax Plus; Alprax Z; Alprine Plus; Alprine-H; Altalin; Altin; Alzex Forte; Alzex Plus; Ambulax-HD; Ambulax-M; Ambulax; Anxit Forte; Anxit Plus; Anzi-P; Ateez-F; Azo-F; Azo-O; Azo-S; Balmusa Plus; Calmtec-P; Cam Plus; Cardilax; Censir Forte; Cooltime; Coral-F; Depten-AZ; Depwell; Destres; Exiten Plus; Faa Plus; Faxtin-A; Fiden-AZ; Fludep Plus; Fludep-AZ; Flumusa; Fluwel; Fluxin-AL; Fluzolam; Kurelam-F; L-Peez F; L-Peez S; Manorest Forte; Manorest Plus; MCalm; Mebasap-AL; Mebrin-AZ; Meloprax; Mentolift-Plus; Resty Forte; Restyl Plus; Stresnil; Zopax Plus; ***Mex.***: Neupax Duo-S.

Pharmacopoeial Preparations

USP 36: Alprazolam Extended-release Tablets; Alprazolam Oral Suspension; Alprazolam Orally Disintegrating Tablets; Alprazolam Tablets.

Amisulpride *(BAN, rINN)*

Amisulpridi; Amisulprid; Amisulprida; Amisulpridas; Amisulpridi; Amisulpridum; Amiszulprid; DAN-216; Амисульприд.

4-Amino-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulphonyl)-2-methoxybenzamide; (*RS*)-4-Amino-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-(ethylsulfonyl)-o-anisamide.

$C_{17}H_{27}N_3O_4S$=369.5

CAS — 71675-85-9.

ATC — N05AL05.

ATC Vet — QN05AL05.

UNII — 8110R6114U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Amisulpride). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane.

Uses and Administration

Amisulpride is a substituted benzamide atypical antipsychotic. It is reported to have a high affinity for dopamine D_2 and D_3 receptors. Amisulpride is used mainly in the management of psychoses such as schizophrenia (below) but in some countries it has also been tried in depression (p. 398.1).

For acute psychotic episodes, a daily dosage of between 400 and 800 mg may be given orally in 2 divided doses increased if necessary to 1.2 g daily. For patients with mainly negative symptoms, daily doses between 50 and 300 mg are recommended. Daily doses of up to 300 mg may be given as a single dose. Amisulpride has also been given by intramuscular injection in doses of 400 mg daily.

Reduced doses are recommended in patients with renal impairment, see below.

Although unlicensed in the UK for use in children and adolescents aged under 18 years, the *BNFC* suggests that those aged from 15 to 18 years may be given the usual oral adult dose of amisulpride for the same indications (see above).

Administration in children. For details of uses and associated doses in adolescents, see Uses and Administration above.

Administration in renal impairment. For patients with renal impairment, the oral dose of amisulpride should be reduced according to creatinine clearance (CC):

- CC between 30 and 60 mL/minute: half the usual dose (see Uses and Administration, above)
- CC between 10 and 30 mL/minute: one-third the usual dose

Similar reductions are also recommended when amisulpride is given intramuscularly.

Schizophrenia. Reviews[1-3] of amisulpride indicate that it may be more effective than classical antipsychotics against general and negative symptoms of schizophrenia (p. 1031.3), and has fewer extrapyramidal adverse effects.

1. Leucht S, *et al.* Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002; **159:** 180–90.

2. Mota Neto JIS, *et al.* Amisulpride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 24/05/05).
3. Pani L, *et al.* Practical issues with amisulpride in the management of patients with schizophrenia. *Clin Drug Investig* 2008; 28: 465–77.

Adverse Effects, Treatment, and Precautions

Although amisulpride may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Insomnia, anxiety, and agitation are common adverse effects with amisulpride. Other less common effects include drowsiness and gastrointestinal disorders such as constipation, nausea, vomiting, and dry mouth. Allergic reactions, abnormal liver function tests, and seizures have been reported rarely.

Hyperprolactinaemia, which may result in galactorrhoea, amenorrhoea, impaired fertility, gynaecomastia, breast pain, and sexual dysfunction, has occurred with amisulpride use. Weight gain has also been noted. Dose-related extrapyramidal dysfunction may occur, but symptoms such as acute dystonia, parkinsonism, and akathisia are generally mild at licensed doses. Tardive dyskinesia has been reported after long-term use and there have been rare cases of neuroleptic malignant syndrome. Hypotension and bradycardia have been reported occasionally; QT prolongation, in rare cases leading to torsade de pointes, has also been noted. The risk of QT prolongation is increased by pre-existing conditions such as bradycardia, hypokalaemia, and congenital or acquired QT prolongation; patients should be reviewed for these conditions before starting amisulpride treatment. Certain medications may also increase the risk (see Interactions, below).

Amisulpride should not be given to patients with phaeochromocytoma or prolactin-dependent tumours. It should be used with caution in patients with severe renal impairment, or a history of epilepsy or Parkinson's disease. The risk of hypotension and sedation is increased in elderly patients.

Amisulpride may affect the performance of skilled tasks including driving.

Withdrawal symptoms have occurred rarely when amisulpride has been stopped abruptly; a gradual dose reduction may be appropriate when stopping amisulpride.

Effects on body-weight. A review[1] has suggested that the risk of weight gain with amisulpride treatment is less than with olanzapine or risperidone, although cases have been reported.[2] The increased risk of weight gain with some atypical antipsychotics is also discussed under Adverse Effects of Clozapine, p. 1059.1.

1. McKeage K, Plosker GL. Amisulpride: a review of its use in the management of schizophrenia. *CNS Drugs* 2004; 18: 933–56.
2. Papadimitriou GN, *et al.* Acute weight gain induced by amisulpride monotherapy in a first-episode schizophrenic patient. *Int Clin Psychopharmacol* 2006; 21: 181–4.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Overdosage. The effects of overdosage of amisulpride in 2 patients have been reported.[1] The first patient had taken about 3 g of amisulpride and an unknown amount of dosulepin and was found to have had a blood-amisulpride concentration of 9.63 micrograms/mL. Generalised convulsions, which resolved spontaneously, were followed by coma, motor restlessness, tachycardia, and slight prolongation of the QT interval. The patient was treated with gastric lavage and had recovered within 48 hours. The second patient, who had been found dead, had a blood-amisulpride concentration of 41.7 micrograms/mL. Severe cardiotoxicity occurred in 4 further cases of amisulpride overdoses of between about 4 and 32 g reported to Australian poisons information centres;[2] all 4 had marked QT prolongation, with bundle branch block or torsade de pointes, and one, who was thought to have ingested between 16 and 24 g, died after cardiac arrest.

1. Tracqui A, *et al.* Amisulpride poisoning: a report on two cases. *Hum Exp Toxicol* 1995; 14: 294–8.
2. Isbister GK, *et al.* Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsades de pointes. *Med J Aust* 2006; 184: 354–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amisulpride as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

Amisulpride should not be given with drugs that may induce arrhythmias (including torsade de pointes); such drugs include some antiarrhythmics, cisapride, thioridazine, erythromycin, and halofantrine. The risk of arrhythmias is also increased with drugs that prolong the QT interval, such as pimozide, haloperidol, and tricyclic antidepressants, and with drugs that produce bradycardia or hypokalaemia, including beta blockers, some calcium-channel blockers, clonidine, digoxin, guanfacine, potassium-depleting diuretics, and lithium; use of these drugs with amisulpride requires caution.

The central effects of other CNS depressants including alcohol may be enhanced by amisulpride. Amisulpride may also enhance the effects of antihypertensive drugs. The dopamine-blocking activity of amisulpride may antagonise the actions of dopaminergics such as levodopa and they should not be given together.

In 7 patients receiving amisulpride, introduction of *lithium* resulted in an average increase of 32% of the dose-corrected plasma concentration of amisulpride.[1] An earlier study had noted that plasma concentrations of amisulpride were raised in patients also taking *clozapine*.[2]

1. Bergemann N, *et al.* Increase in plasma concentrations of amisulpride after receiving co-medication with lithium. *Pharmacopsychiatry* 2005; 38: 44.
2. Bergemann N, *et al.* Plasma amisulpride levels in schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol* 2004; 14: 245–50.

Pharmacokinetics

Amisulpride is absorbed from the gastrointestinal tract but bioavailability is reported to be only about 48%. An initial peak in plasma concentration has been reported to occur 1 hour after oral doses and a second higher peak after 3 to 4 hours. Plasma protein binding is reported to be only about 16%. Metabolism is limited, with most of a dose appearing in the urine as unchanged drug. The terminal elimination half-life is about 12 hours.

References.

1. Rosenzweig P, *et al.* A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol* 2002; 17: 1–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Enorden; *Austral.*: Amipride; Solian; Sulprix; *Austria*: Solian; *Belg.*: Solian; *Braz.*: Socian; *Chile*: Socian; *China*: Solian (泰里昂); *Cz.*: Amilia; Deniban; Solian; *Denm.*: Amitrex†; Solian; *Fr.*: Solian; *Ger.*: Amisulid†; Solian; *Gr.*: Goldalian; Isofredil; Matil; Nodasic; Prilarem; Solamid; Solian; Sulpisal; Zoloser; *Hong Kong*: Solian; *Hung.*: Amiprid; Amitrex; Asulpan; *India*: Amgrace; Amigold; Goldpride; *Irl.*: Solian; *Israel*: Solian; *Ital.*: Deniban; Solian; Sulamid; *Malaysia*: Solian; *Mex.*: Solian; *Norw.*: Solian; *NZ*: Solian; *Philipp.*: Solian; *Pol.*: Amisan; Solian; *Port.*: Amitrex; Socian; *Rus.*: Lymipranil (Лимипранил); Solian (Солиан); *S.Afr.*: Solian; *Singapore*: Solian; *Spain*: Aracalm; Misulmylan†; Solian; *Switz.*: Solian; *Turk.*: Paxiprid; Solian; *UK*: Solian; *Ukr.*: Soleron (Солерон); Solian (Солиан).

Pharmacopoeial Preparations
BP 2014: Amisulpride Oral Solution; Amisulpride Tablets.

Amobarbital (BAN, rINN)

Amobarbitaali; Amobarbital; Amobarbitalis; Amobarbitalum; Amylobarbitone; Pentymalum; Амобарбитал.

5-Ethyl-5-isopentylbarbituric acid.

$C_{11}H_{18}N_2O_3$=226.3

CAS — 57-43-2.

ATC — N05CA02.

ATC Vet — QN05CA02.

UNII — GWH6LI239E.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of amobarbital:

Amys; Birds; Blue; Blue angels; Blue birds; Blue bullets; Blue clouds; Blue devils; Blue dolls; Blue heaven; Blue heavens; Blues.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Amobarbital). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol; soluble in dichloromethane. Forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Amobarbital Sodium (BANM, rINNM)

Amobarbitaalinatrium; Amobarbital-Natrium; Amobarbital sódico; Amobarbital sodique; Amobarbital sodná sůl; Amobarbitalio natrio druska; Amobarbitalnatrium; Amobarbitál-nátrium; Amobarbitalum Natricum; Amylobarbitone Sodium; Barbamylum; Natrii Amobarbitalum; Pentymalnatrium; Sodium Amobarbital; Soluble Amylobarbitone; Натрий Амобарбитал.

Sodium 5-ethyl-5-isopentylbarbiturate.

$C_{11}H_{17}N_2NaO_3$=248.3

CAS — 64-43-7.

ATC — N05CA02.

ATC Vet — QN05CA02.

UNII — G0313KNC7D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Jpn includes Amobarbital Sodium for Injection.

Ph. Eur. 8: (Amobarbital Sodium). A white or almost white, hygroscopic, granular powder. Very soluble in carbon dioxide-free water (a small fraction may be insoluble); freely soluble in alcohol. A 10% solution in water has a pH of not more than 11.0. Store in airtight containers.

USP 36: (Amobarbital Sodium). A white, odourless, hygroscopic, friable, granular powder. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. Solutions decompose on standing; decomposition is accelerated by heat. pH of a 10% solution in water is not more than 11.0. Store in airtight containers.

Incompatibility. Amobarbital may be precipitated from preparations containing amobarbital sodium, depending on the concentration and pH. Amobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Uses and Administration

Amobarbital is a barbiturate that has been used as a hypnotic and sedative. Its use can no longer be recommended because of its adverse effects and risk of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p. 1033.2) in patients already taking it. Amobarbital sodium has been used parenterally for premedication in anaesthetic procedures (p. 1899.1) although barbiturates for pre-operative sedation have generally been replaced by other drugs. It has also been used to control refractory tonic-clonic status epilepticus (p. 510.2) although the short-acting barbiturate thiopental is preferred.

The usual oral dose of amobarbital for insomnia was 100 to 200 mg of the base or 60 to 200 mg of the sodium salt, taken at bedtime. A more rapid onset of effect was obtained with the sodium salt.

Barbiturates with a longer action such as phenobarbital (p. 535.2) are still used in epilepsy and those with a shorter action such as methohexital (p. 1909.3) or thiopental (p. 1918.2) for anaesthesia.

General references.

1. López-Muñoz F, *et al.* The history of barbiturates a century after their clinical introduction. *Neuropsychiatr Dis Treat* 2005; 1: 329–43.

Cerebrovascular disorders. For mention of the use of barbiturate-induced coma in the management of patients with cerebral ischaemia or raised intracranial pressure, see under Pentobarbital, p. 1095.1.

Wada test. The Wada test, also known as the intracarotid amobarbital procedure, in which amobarbital sodium is injected into one internal carotid artery, has been used to assess brain function associated with one cerebral hemisphere and has typically been used for pre-operative screening of candidates for epilepsy surgery. However, with the advent of safer non-invasive techniques, its continued use has been questioned.[1,2]

1. Baxendale SA, *et al.* Evidence-based practice: a reevaluation of the intracarotid amobarbital procedure (Wada test). *Arch Neurol* 2008; 65: 841–5.
2. Baxendale S. The Wada test. *Curr Opin Neurol* 2009; 22: 185–9.

Dependence and Withdrawal of Barbiturates

The development of dependence is a high risk with amobarbital and other barbiturates and may occur after regular use even in therapeutic doses for short periods. Barbiturates should not therefore be stopped abruptly, but should be withdrawn by gradual reduction of the dose over a period of days or weeks. A long-acting barbiturate such as phenobarbital may be substituted for a short- or intermediate-acting one, followed by gradual reduction of the phenobarbital dose.

Withdrawal symptoms are similar to those of alcohol withdrawal but can be more severe. Minor symptoms may appear 8 to 12 hours after the last dose, usually in the following order: anxiety, muscle twitching, tremors of hands and fingers, progressive weakness, dizziness, distortion in visual perception, nausea, vomiting, insomnia, and orthostatic hypotension. Convulsions, hallucinations, and delirium may occur within 16 hours and last up to 5 days after stopping barbiturates abruptly. The intensity of withdrawal symptoms gradually declines over about 15 days. Fatalities due to cardiovascular collapse have occurred.

References.

1. Loder E, Biondi D. Oral phenobarbital loading: a safe and effective method of withdrawing patients with headache from butalbital compounds. *Headache* 2003; 43: 904–9.
2. Mauskop A. Simplified butalbital withdrawal protocol. *Headache* 2004; 44: 290–1.

Adverse Effects

Drowsiness and sedation are the most frequent adverse effects of amobarbital and other barbiturates and are a consequence of dose-related CNS depression. Other adverse effects include respiratory depression, headache, gastrointestinal disturbances, ataxia, agitation, confusion, and abnormal thinking. Paradoxical excitement and irritability may occur, particularly in children, the elderly, and patients in acute pain. Hypersensitivity reactions occur rarely and include rashes (erythema multiforme and exfoliative dermatitis, sometimes fatal, have been reported), hepatitis and cholestasis, and photosensitivity. Blood disorders, including megaloblastic anaemia after chronic use of barbiturates, have also occurred occasionally.

Neonatal intoxication, drug dependence, and symptoms resembling vitamin-K deficiency have been reported in infants born to mothers who received barbiturates during pregnancy. Congenital malformations have been reported in children of women who took barbiturates during pregnancy, but the causal role has been debated.

Nystagmus, miosis, hyporeflexia or areflexia, dysarthria, and ataxia may occur with excessive doses of barbiturates. The toxic effects of overdosage result from profound CNS depression and include coma, respiratory and cardiovascular depression, with hypotension and shock leading to renal failure and death. Hypothermia may occur with subsequent pyrexia on recovery. Erythematous or haemorrhagic blisters reportedly occur in about 6% of patients, but are not characteristic solely of barbiturate poisoning.

Solutions of the sodium salts of barbiturates are extremely alkaline, and tissue necrosis has followed accidental intra-arterial injection or extravasation. Thrombophlebitis, pain, and injury to adjacent nerves can occur at the site of injection. Intravenous injection may be hazardous; hypotension, shock, severe respiratory depression, laryngospasm, and apnoea have occurred particularly after rapid injection.

Overdosage. A detailed review of drug-induced stupor and coma, including that caused by barbiturates.[1]

1. Ashton CH, *et al.* Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; 8: 1–39.

Treatment of Adverse Effects

After an overdose of a barbiturate, endotracheal intubation may be necessary if the patient is unconscious. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with barbiturates to be uncertain. However, it is suggested that oral activated charcoal may be considered in adults and children if this is given within 1 hour of ingestion and the quantity of barbiturate exceeds the following amount:

- amobarbital: 4 mg/kg
- barbital: 4 mg/kg
- butobarbital: 6 mg/kg
- cyclobarbital: 8 mg/kg
- methylphenobarbital: 7 mg/kg
- phenobarbital: 4 mg/kg

Activated charcoal is also recommended in children and treatment-naive adults who have ingested any amount of pentobarbital or secobarbital, and in those adults who are taking the drugs, if the usual daily dose or 5 mg/kg has been exceeded. Patients who have ingested any amount of thiopental or veterinary preparations of pentobarbital or secobarbital should be given activated charcoal. Repeat doses of activated charcoal are useful in enhancing the elimination of phenobarbital and should be considered in patients who are experiencing severe symptoms following an overdose, such as coma or cardiovascular or respiratory collapse; care should be taken to protect the airway. Repeat doses may also be warranted in overdoses involving drugs such as methylphenobarbital and primidone that are metabolised to phenobarbital. In addition, patients should be managed with intensive supportive therapy, with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions, and to the maintenance of the electrolyte balance. Charcoal haemoperfusion or haemodialysis should be considered in severe cases.

Precautions

Because of their adverse effects and risk of dependence the use of barbiturates as hypnotics and sedatives can no longer be recommended (but see Uses and Administration, p. 1037.3).

Amobarbital and other barbiturates are best avoided in elderly and debilitated patients, in young adults, in children, and in those with depression or a history of drug or alcohol addiction or abuse.

Amobarbital is contra-indicated in patients with pulmonary insufficiency, sleep apnoea, pre-existing CNS depression or coma, and severe hepatic impairment, and should be given with caution to those with renal impairment. Barbiturates given to patients in pain may provoke a paradoxical excitatory reaction, unless an analgesic is also given. With continued use, tolerance develops to the sedative or hypnotic effects of the barbiturates to a greater extent than to their lethal effects. Barbiturates may cause drowsiness which may persist the next day; affected patients should not drive or operate machinery.

See Adverse Effects, above, for the hazards of giving barbiturates during pregnancy and Breast Feeding, below, for cautions on their use in nursing mothers.

Dependence readily develops after use of barbiturates with a **withdrawal syndrome** if stopped abruptly (see Dependence and Withdrawal, above).

Barbiturates are abused for their euphoriant effects.

Breast feeding. Small amounts of barbiturates are distributed into breast milk, and most authorities, such as the *BNF*, consider that they should not be taken while breast feeding. The last available guidance from the American Academy of Pediatrics noted[1] that the long-acting antiepileptic barbiturate, phenobarbital, has been associated with significant effects on some nursing infants, although it suggests that some other barbiturates may be compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Interactions

Sedation or respiratory depression with barbiturates may be enhanced by drugs with CNS-depressant properties; in particular alcohol should be avoided. Barbiturates generally induce liver microsomal enzymes, and thus increase the rate of metabolism (and decrease the activity) of many other drugs as well as endogenous substances. Continued use may result in induction of their own metabolism. MAOIs may prolong the CNS depressant effects of some barbiturates, probably by inhibition of their metabolism. However, MAOIs, like other antidepressants, also reduce the convulsive threshold and thereby antagonise the anticonvulsant action of barbiturates.

For some further interactions involving barbiturates, see under Phenobarbital, p. 537.2.

Pharmacokinetics

Amobarbital is readily absorbed from the gastrointestinal tract and is rapidly distributed to all tissues and fluids. It is about 60% bound to plasma proteins. It has a half-life of about 20 to 25 hours, which is considerably extended in neonates. It crosses the placenta and small amounts are distributed into breast milk. Amobarbital is metabolised in the liver; up to about 50% is excreted in the urine as 3′-hydroxyamylobarbital and up to about 30% as *N*-hydroxyamylobarbital, with less than 1% appearing unchanged. Up to about 5% is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Amytal; *Jpn*: Isomytal; *Thai.*: Amytal; *UK*: Amytal; *USA*: Amytal†.

Multi-ingredient Preparations. *Arg.*: Cuait N†; *Hong Kong*: Alubar†; Alutal†; Amiton†; *S.Afr.*: Repasma†; *Thai.*: Ama; *UK* Tuinal; *USA*: Tuinal.

Pharmacopoeial Preparations

USP 36: Amobarbital Sodium for Injection; Secobarbital Sodium and Amobarbital Sodium Capsules.

Amperozide *(BAN, rINN)*

Amperozida; Ampérozide; Amperozidum; FG-5606; Амперозид.

4-[4,4-Bis(4-fluorophenyl)butyl]-*N*-ethylpiperazine-1-carboxamide.

$C_{23}H_{29}F_2N_3O$=401.5

CAS — 75558-90-6 (amperozide); 75529-73-6 (amperozide hydrochloride).

ATC Vet — QN05AX90.

UNII — 0M2W3TAG39.

Profile

Amperozide is an antipsychotic that has been used in veterinary medicine.

Aripiprazole *(BAN, USAN, rINN)*

Aripiprazol; Aripiprazolum; OPC-31; OPC-14597; Арипипразол.

7-[4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one.

$C_{23}H_{27}Cl_2N_3O_2$=448.4

CAS — 129722-12-9.

ATC — N05AX12.

ATC Vet — QN05AX12.

UNII — 82VFR53I78.

Pharmacopoeias. In *US*.

USP 36: (Aripiprazole). A white to off-white, crystalline powder. Insoluble in water and in methyl alcohol; freely soluble in dichloromethane; sparingly soluble in toluene Store in airtight containers at a temperature of 25 degrees excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Aripiprazole is an atypical antipsychotic that has serotonin 5-HT_{1A}-receptor partial agonist and 5-HT_{2A}-receptor antagonist properties as well as being a partial agonist at dopamine D_2 receptors. It is used in the management of schizophrenia and of bipolar disorder. Aripiprazole is also used as an adjunct in the treatment of depression. (See Psychiatric Disorders, p. 1039.1.) Aripiprazole is usually given orally or by intramuscular injection as the anhydrous substance. The longer-acting monohydrate polymorphous form is given by intramuscular injection. For all routes doses are expressed in terms of the equivalent amount of the anhydrous substance; aripiprazole monohydrate 104 mg is equivalent to about 100 mg of anhydrous aripiprazole.

For the treatment of **schizophrenia**, aripiprazole is given in an initial oral dose of 10 or 15 mg once daily. The usual maintenance dose is 15 mg once daily although the dose may be adjusted at intervals of not less than 2 weeks up to a maximum of 30 mg daily.

For the treatment of *acute manic or mixed episodes* in **bipolar disorder**, a recommended initial oral dose is 15 mg once daily as monotherapy, or 10 or 15 mg if given as an adjunct to lithium or valproate; this may subsequently be increased to 30 mg once daily according to response. For the *maintenance treatment* of bipolar disorder, patients should be continued on the same dose on which they were stabilised

Aripiprazole (as the anhydrous substance) may be given by deep intramuscular injection for acute agitation in patients with schizophrenia or bipolar mania. The recommended initial dose is 9.75 mg although some patients may only need 5.25 mg and others up to 15 mg. If necessary, further doses may be given after at least 2 hours up to a maximum total daily dose of 30 mg. Patients should be switched to oral therapy as soon as possible if ongoing treatment is required. The long-acting depot preparation (aripiprazole monohydrate) may also be given by deep intramuscular gluteal injection once every month for maintenance therapy of schizophrenia. Patients with no history of aripiprazole use should initially be treated with aripiprazole orally to assess tolerability and response. The recommended initial and maintenance dose is a single monthly injection of 400 mg (no sooner than 26 days after the previous injection). Oral antipsychotic therapy should be continued for the first 14 days after the first injection. The dose may be reduced to 300 mg monthly if adverse effects occur.

As adjunctive therapy in **depression**, US licensed product information recommends an initial oral dose of 2 to 5 mg once daily; the dose may be adjusted in increments o

up to 5 mg at intervals of not less than 1 week to a maximum of 15 mg daily. The usual recommended dose is 5 to 10 mg once daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, below for further details. Adjustments may also be needed in those who are poor CYP2D6 metabolisers (see Administration in Genetic Variation, below).

For details of uses and associated doses in children and adolescents, see below.

Administration in children. In the USA, aripiprazole is licensed for the treatment of:
- schizophrenia in adolescents aged 13 to 17 years
- bipolar disorder in those aged 10 to 17 years
- irritability associated with autistic disorder in those aged 6 to 17 years

In the UK, aripiprazole is licensed for the treatment of:
- schizophrenia in adolescents aged 15 years and older
- acute manic episodes associated with bipolar disorder in those aged 13 years and older

NICE recommends aripiprazole as an option for the treatment of schizophrenia in 15- to 17-year-olds who are intolerant of, or have an inadequate response or contra-indications to risperidone.[1] (It was noted that risperidone is considered the most widely used first-line atypical antipsychotic in the UK for adolescents with schizophrenia although such use is unlicensed.)

For **schizophrenia** or *acute manic or mixed episodes* in **bipolar disorder**, the recommended initial oral dose is 2 mg daily increased to 5 mg daily after 2 days and then to the target dose of 10 mg daily after another 2 days; any subsequent dose increases should be made in 5-mg increments up to a total maximum dose of 30 mg daily. For the *maintenance treatment* of bipolar disorder, patients should be continued on the same dose on which they were stabilised. Aripiprazole may be given as monotherapy, or as an adjunct to lithium or valproate, in bipolar disorder.

For the treatment of **irritability associated with autistic disorder**, the recommended initial oral dose is 2 mg daily increased to 5 mg daily; if necessary, the dose may be adjusted in increments of up to 5 mg at intervals of not less than 1 week to a maximum of 15 mg daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, below for further details. Adjustments may also be needed in those who are poor CYP2D6 metabolisers (see Administration in Genetic Variation, below).

1. NICE. Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years: Technology Appraisal Guidance 213 (issued January 2011). Available at: http://www.nice.org.uk/nicemedia/live/13317/52608/52608.pdf (accessed 28/03/13)

Administration in genetic variation. The dose of oral and intramuscular aripiprazole (anhydrous) should be reduced to *half* the usual dose (see *Uses and Administration*, p. 1038.3) in patients who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2D6; a quarter of the usual dose should be given to those who are also taking potent CYP3A4 inhibitors.

The monthly dose of the long-acting intramuscular preparation (aripiprazole monohydrate) should be reduced to 300 mg in poor CYP2D6 metabolisers; those who are also taking CYP3A4 inhibitors for longer than 14 days should be given 200 mg.

Psychiatric disorders. Aripiprazole is used in the management of *schizophrenia* (p. 1031.3).[1-7] Although data are scanty, systematic reviews[1-3] have concluded that aripiprazole does not have significant advantages over other atypical and classical antipsychotics in the treatment of schizophrenia. However, it was found to be better tolerated, including a lower risk for hyperprolactinaemia and QT interval prolongation compared with other atypical antipsychotics.

Aripiprazole is also used in patients with *bipolar disorder* (p. 397.2)[7-9] and as an adjunct in the treatment of *depression* (p. 398.1).[10] It is used for the treatment of irritability associated with *autistic disorder* in children and adolescents.[11,12]

1. El-Sayeh HGG, Morganti C. Aripiprazole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 15/05/06).
2. Bhattacharjee J, El-Sayeh HGG. Aripiprazole versus typical antipsychotic drugs for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 29/05/09).
3. Khanna P, *et al.* Aripiprazole versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2013 (accessed 06/06/13).
4. Belgamwar RB, El-Sayeh HGG. Aripiprazole versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2011 (accessed 06/06/13).
5. NICE. Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years: Technology Appraisal Guidance 213 (issued January 2011). Available at: http://www.nice.org.uk/nicemedia/live/13317/52608/52608.pdf (accessed 07/06/13)
6. Croxtall JD. Aripiprazole: a review of its use in the management of schizophrenia in adults. *CNS Drugs* 2012; 26: 155–83.
7. Doey T. Aripiprazole in pediatric psychosis and bipolar disorder: a clinical review. *J Affect Disord* 2012; 138 (suppl): S15–S21.
8. Dhillon S. Aripiprazole: a review of its use in the management of mania in adults with bipolar I disorder. *Drugs* 2012; 72: 133–62.
9. NICE. Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder: Technology Appraisal Guidance 292 (issued July 2013). Available at: http://www.nice.org.uk/nicemedia/live/14225/64565/64565.pdf (accessed 29/11/13)
10. Pae CU, *et al.* Aripiprazole as adjunctive therapy for patients with major depressive disorder: overview and implications of clinical trial data. *CNS Drugs* 2011; 25: 109–27.
11. Curran MP. Aripiprazole: in the treatment of irritability associated with autistic disorder in pediatric patients. *Paediatr Drugs* 2011; 13: 197–204.
12. Ching H, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2012 (accessed 06/06/13).

Adverse Effects, Treatment, and Precautions

Although aripiprazole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Common adverse effects with aripiprazole include gastrointestinal disorders such as constipation, dyspepsia, nausea, and vomiting, headache, anxiety, insomnia, lightheadedness, and drowsiness. Weight gain has been reported; however, this appears to be slight. Blood dyscrasias including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia may occur. The incidence of extrapyramidal effects with aripiprazole is low with akathisia being most commonly reported. Tardive dyskinesia has been reported infrequently and there have been a few cases of neuroleptic malignant syndrome. Pathological gambling has also been reported.

Tachycardia and orthostatic hypotension are uncommon with aripiprazole treatment; bradycardia, ventricular arrhythmias, cardiac arrest, and sudden unexplained death have been reported very rarely as have QT prolongation and torsade de pointes. Nonetheless aripiprazole should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension.

Seizures are rare with aripiprazole but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

When aripiprazole is used as an adjunct in depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1.

Aripiprazole may affect the performance of skilled tasks including driving.

References.
1. Pae CU. A review of the safety and tolerability of aripiprazole. *Expert Opin Drug Safety* 2009; 8: 373–86.
2. Kirino E. Efficacy and safety of aripiprazole in child and adolescent patients. *Eur Child Adolesc Psychiatry* 2012; 21: 361–8.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.
1. McQuade RD, *et al.* A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004; 65 (suppl 18): 47–56.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Licensed product information for aripiprazole also includes a warning about evidence of a dose-response relationship between cerebrovascular adverse events and the use of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease.

Overdosage. The manufacturer has reported that patients have taken estimated overdoses of up to 1080 mg of aripiprazole with no fatalities. Signs and symptoms have included nausea, vomiting, asthenia, diarrhoea, and somnolence. In one report a 27-year-old woman who ingested 330 mg of aripiprazole with cyclobenzaprine 10 mg and quetiapine 25 mg was found to be drowsy but easily rousable 50 minutes later.[1] Initial treatment consisted of oral activated charcoal; recovery was subsequently uneventful. Serum concentrations of aripiprazole and its main metabolite dehydro-aripiprazole, measured 195 minutes after ingestion, were 596 nanograms/mL and 120 nanograms/mL, respectively. In another report[2] a 2½-year-old child vomited and became lethargic within 1 hour of taking 195 mg of aripiprazole (17.1 mg/kg). Activated charcoal was given 3 hours after ingestion but she subsequently became unconscious. However, respiratory support was not required and the child gradually regained consciousness over the next 24 hours. Symptoms of somnolence, ataxia, and tremulousness resolved over 7 days. The serum concentration of aripiprazole plus dehydro-aripiprazole was 1873 nanograms/mL 10 hours after ingestion.

1. Carstairs SD, Williams SR. Overdose of aripiprazole, a new type of antipsychotic. *J Emerg Med* 2005; 28: 311–13.
2. Seifert SA. Aripiprazole (Abilify®) overdose in a 2.5 year-old. *J Toxicol Clin Toxicol* 2003; 41: 647–8.

Pregnancy. For comments on the use of some atypical antipsychotics, including aripiprazole, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Licensed product information states that aripiprazole showed possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Aripiprazole should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

The central effects of other CNS depressants including alcohol may be enhanced by aripiprazole. Aripiprazole may also enhance the effects of antihypertensive drugs. It should be used with caution in patients also receiving drugs that prolong the QT interval or cause electrolyte imbalance.

Aripiprazole is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Potent inhibitors of CYP3A4, such as ketoconazole, or of CYP2D6, such as quinidine, can increase aripiprazole plasma concentrations. Conversely, potent CYP3A4 inducers, such as carbamazepine, can reduce plasma concentrations of aripiprazole. Dose adjustment of aripiprazole (anhydrous) is usually recommended when it is given with such drugs:
- potent inhibitors of CYP2D6: reduce to half the usual dose (see Uses and Administration, p. 1038.3); however, dose reduction is not necessary when aripiprazole is used for adjunctive treatment of depression
- potent inhibitors of CYP3A4: reduce to half the usual dose
- a combination of potent, moderate, or weak inhibitors of CYP2D6 and of CYP3A4: reduce to a quarter of the usual dose
- potent inducers of CYP3A4: increase to double the usual dose

The monthly dose of the long-acting preparation (aripiprazole monohydrate) should only be reduced in patients taking these isoenzyme inhibitors for longer than 14 days, as follows:
- patients receiving 400 mg monthly of aripiprazole and also taking:
  - potent CYP2D6 *or* CYP3A4 inhibitors: reduce to 300 mg
  - CYP2D6 *and* CYP3A4 inhibitors: reduce to 200 mg
- patients receiving 300 mg monthly of aripiprazole and also taking:
  - potent CYP2D6 *or* CYP3A4 inhibitors: reduce to 200 mg
  - CYP2D6 *and* CYP3A4 inhibitors: reduce to 160 mg

The use of CYP3A4 inducers for longer than 14 days should be avoided.

Antiepileptics. For a report of Stevens-Johnson syndrome occurring on use of aripiprazole with *lamotrigine*, see p. 530.2.

Pharmacokinetics

Aripiprazole is well absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur in about 3 to 5 hours. After intramuscular injection, peak plasma concentrations occur between 1 to 3 hours. Bioavailability is reported to be 87% with oral tablets and 100% with the intramuscular injection; it is widely distributed. Aripiprazole is metabolised mainly in the liver and pathways involved include dehydrogenation and hydroxylation, via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and *N*-dealkylation, via CYP3A4. The major metabolite, dehydro-aripiprazole, is also active and represents about 40% of the plasma levels of aripiprazole. The mean elimination half-lives of aripiprazole

and dehydro-aripiprazole are about 75 and 95 hours, respectively; in a minority of poor metabolisers the half-life of aripiprazole may be extended to about 146 hours. Protein binding of aripiprazole and its major metabolite is about 99%, mainly to albumin. Elimination is mostly in the faeces (about 55%), with about 25% of a dose appearing in the urine, mainly in the form of metabolites.

It is distributed into breast milk.

References.
1. Mallikaarjun S, *et al.* Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *J Clin Pharmacol* 2004; **44**: 179–87.
2. Boulton DW, *et al.* Pharmacokinetics and tolerability of intramuscular, oral and intravenous aripiprazole in healthy subjects and in patients with schizophrenia. *Clin Pharmacokinet* 2008; **47**: 475–85.
3. Mallikaarjun S, *et al.* Effects of hepatic or renal impairment on the pharmacokinetics of aripiprazole. *Clin Pharmacokinet* 2008; **47**: 533–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Arixind; Arlemide; Groven†; Irazem; Lemidal; Siblix; *Austral.*: Abilify; *Austria*: Abilify; *Belg.*: Abilify; *Braz.*: Abilify; *Canad.*: Abilify; *Chile*: Abilify; Arilex; Azymol; Ilimit; Labosol; Viza; *China*: Abilify (安律凡); An Lv Fan (安律凡)†; Ao Pai (奥派); Brisking (博思清); *Cz.*: Abilify; *Denm.*: Abilify; *Fin.*: Abilify; *Fr.*: Abilify; *Ger.*: Abilify; *Gr.*: Abilify; *Hong Kong*: Abilify; *Hung.*: Abilify; *India*: Arena; Aria; Aridus; Arilan; Arip-MT; Aripat-MD; Aripra-MT; Arive; Arpicin; Arpizol; Arza; Arzu; Asprito; Elrip; Real One; *Indon.*: Abilify; *Irl.*: Abilify; *Israel*: Abilify; Ariply; *Ital.*: Abilify; *Jpn*: Abilify; *Malaysia*: Abilify; *Mex.*: Abilify; *Neth.*: Abilify; *Norw.*: Abilify; *NZ*: Abilify; *Philipp.*: Abilify; *Pol.*: Abilify; *Port.*: Abilify; *Rus.*: Abilify (Абилифай); *S.Afr.*: Abilify; *Singapore*: Abilify; *Spain*: Abilify; *Swed.*: Abilify; *Switz.*: Abilify; *Thai.*: Abilify; *Turk.*: Abilify; Abizol; Ignis; *UK*: Abilify; *USA*: Abilify; *Venez.*: Abilify.

Asenapine Maleate *(BANM, USAN, rINNM)*

Asénapine, Maléate d'; Asenapini Maleas; Maleato de asenapina; Org-5222; Асенапина Малеат.

(3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1)

$C_{17}H_{16}ClNO.C_4H_4O_4$=401.8

CAS — 65576-45-6 (asenapine); 85650-56-2 (asenapine maleate).

ATC — N05AH05.

ATC Vet — QN05AH05.

UNII — CU9463U2E2.

Uses and Administration

Asenapine maleate is an atypical antipsychotic reported to be an antagonist at various serotonin and dopamine receptors, as well as at adrenergic (α_1 and α_2) and histamine (H_1 and H_2) receptors. It is used in the management of schizophrenia (p. 1031.3) and of bipolar disorder (p. 397.2).

Asenapine is given sublingually as the maleate although doses are expressed in terms of the base; 7 mg of asenapine maleate is equivalent to about 5 mg of asenapine. Eating and drinking should be avoided for 10 minutes after taking asenapine.

The usual initial and target dose for the *acute* treatment of **schizophrenia** is the equivalent of 5 mg of the base twice daily. This dose may also be used for *maintenance treatment* although a dose of 10 mg twice daily may be required by some patients if tolerated.

When used as monotherapy in the *acute treatment of mixed or manic episodes* associated with **bipolar disorder**, the initial and maintenance dose is 10 mg twice daily; this may be reduced to 5 mg twice daily if adverse effects occur. The initial dose when used as adjunctive therapy with either lithium or valproate, is 5 mg twice daily; this may be increased to 10 mg twice daily depending on the clinical response and tolerability.

References.
1. Potkin SG, *et al.* Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 2007; **68**: 1492–1500.
2. Weber J, McCormack PL. Asenapine. *CNS Drugs* 2009; **23**: 781–92.
3. McIntyre RS, *et al.* Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 2010; **122**: 27–38.
4. Schoemaker J, *et al.* Long-term assessment of asenapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry* 2010; **43**: 138–46.
5. Kane JM, *et al.* A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry* 2011; **72**: 349–55.

Adverse Effects, Treatment, and Precautions

Although asenapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with asenapine include somnolence, dizziness, and oral hypoaesthesia. Other common adverse effects include gastrointestinal disorders, fatigue, irritability, anxiety, and weight increase. Neuroleptic malignant syndrome and extrapyramidal symptoms such as tardive dyskinesia and akathisia have also been reported. Local reactions associated with its sublingual use include mucosal ulceration, blistering, and inflammation, which may be severe enough to stop therapy. Systemic hypersensitivity reactions have also occurred.

Hyperprolactinaemia, which may result in galactorrhoea, amenorrhoea, gynaecomastia, and impotence, has occurred with asenapine. Blood dyscrasias including leucopenia, neutropenia, and thrombocytopenia may occur.

Orthostatic hypotension and syncope have been reported with asenapine, particularly in early treatment; QT prolongation, which in rare cases can lead to torsade de pointes, has also been noted. Asenapine should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension; in addition, it should be avoided in those with a history of arrhythmias or other conditions that may increase the risk of QT prolongation including bradycardia or hypokalaemia. Certain medications may also increase the risk (see Interactions, below).

Seizures may occasionally occur with asenapine and it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold. Asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh class C).

Asenapine may affect the performance of skilled tasks including driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Hypersensitivity. An FDA review[1] of its Adverse Event Reporting System (AERS) database from approval in August 2009 up to September 2010 identified 52 cases of type I hypersensitivity reactions associated with asenapine; 8 cases had reported after the first dose. Symptoms reported included anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnoea, wheezing, and rash.

1. FDA. Drug safety communication: serious allergic reactions reported with the use of Saphris (asenapine maleate) (issued 1st September, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm270243.htm (accessed 17/01/12)

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants including alcohol may be enhanced by asenapine. Asenapine is also an α_1-adrenergic antagonist and may enhance the effects of certain antihypertensive drugs. There may be a risk of QT prolongation when asenapine is given with other drugs that are known to cause this effect. Asenapine can antagonise the effects of dopaminergics.

The metabolism of asenapine is mediated mainly by uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) and the cytochrome P450 isoenzymes (in particular CYP1A2). Use with drugs that inhibit, induce, or act as a substrate to these enzyme pathways may affect plasma concentrations of asenapine: fluvoxamine, a CYP1A2 inhibitor, may significantly increase the plasma levels of asenapine. Asenapine, itself, is a weak inhibitor of CYP2D6, and should be given cautiously with drugs such as paroxetine that are both substrates and inhibitors of CYP2D6.

Pharmacokinetics

Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. Its bioavailability is reduced by food and drink. Plasma protein binding is high (95%). Metabolism of asenapine is mainly through direct glucuronidation by uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) and oxidation by cytochrome P450 isoenzymes (mainly CYP1A2). The mean terminal half-life is about 24 hours. Asenapine is excreted in the urine (about 50%) and faeces (about 40%); only a small amount is excreted unchanged.

Asenapine is thought to be distributed into breast milk on the basis of studies in *rats*.

References.
1. Peeters P, *et al.* Asenapine pharmacokinetics in hepatic and renal impairment. *Clin Pharmacokinet* 2011; **50**: 471–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Saphris; *Belg.*: Sycres; *Braz.*: Saphris; *Canad.*: Saphris; *Cz.*: Sycrest; *Denm.*: Sycres; *Fr.*: Sycrest; *Ger.*: Sycrest; *Israel*: Saphris; *Neth.*: Sycres; *Norw.*: Sycrest; *Pol.*: Sycrest; *Port.*: Sycrest; *Singapore*: Saphris; *Spain*: Sycrest; *Switz.*: Sycrest; *UK*: Sycrest; *USA*: Saphris.

Avizafone *(BAN, rINN)*

Avizafona; Avizafonum; Prodiazepam; Ro-03-7355; Ro-03-7355/000; Ro-03-7355/002 (avizafone hydrochloride); Авизафон.

L-Lysyl-(2′-benzoyl-4′-chloro-*N*′-methyl)glycinanilide.

$C_{22}H_{27}ClN_4O_3$=430.9

CAS — 65617-86-9 (avizafone); 60067-16-5 (avizafone hydrochloride).

UNII — 65NK71K78P.

Profile

Avizafone is rapidly metabolised in the body to diazepam (p. 1063.2) and is included as the anticonvulsant component of an intramuscular injection used by military personnel as an antidote to nerve agents. The usual dose of avizafone given in this preparation is 10 mg, repeated every 15 minutes if necessary up to a total dose of 30 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Nerve Agent Antidote L4A1.

Azaperone *(BAN, USAN, rINN)*

Atsaperoni; Azaperon; Azaperona; Azapérone; Azaperonum R-1929; Азанерон.

4′-Fluoro-4-[4-(2-pyridyl)piperazin-1-yl]butyrophenone.

$C_{19}H_{22}FN_3O$=327.4

CAS — 1649-18-9.

ATC Vet — QN01AX91; QN05AD90.

UNII — 198V78AK7W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Azaperone for Veterinary Use; Azaperone B (Vet) 2014). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Azaperone). M.p. 92 degrees to 95 degrees. Protect from light.

Profile

Azaperone is a butyrophenone antipsychotic used as a tranquilliser in veterinary medicine.

Barbital *(BAN, rINN)*

Barbitaali; Barbitál; Barbitalis; Barbitalum; Barbitone; Diemalum; Diethylmalonylurea; Барбитал.

5,5-Diethylbarbituric acid.

$C_8H_{12}N_2O_3$=184.2

CAS — 57-44-3.

ATC — N05CA04.

ATC Vet — QN05CA04.

UNII — SWZS3ENE2P.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Barbital). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; soluble in boiling water and in alcohol. It forms water-

soluble compounds with alkali hydroxides and carbonates and with ammonia.

Barbital Sodium *(BANM, rINN)*

Barbital de sodio; Barbital sódico; Barbital sodique; Barbital sodowy; Barbitalum Natricum; Barbitone Sodium; Diemalnatrium; Soluble Barbitone; Барбитал Натрий.

Sodium 5,5-diethylbarbiturate.

$C_8H_{11}N_2NaO_3$=206.2

CAS — 144-02-5.

ATC — N05CA04.

ATC Vet — QN05CA04.

UNII — 275L5M93QS.

Profile

Barbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It was formerly used for its hypnotic and sedative properties but barbiturates are no longer considered appropriate for such purposes.

Benperidol *(BAN, USAN, rINN)*

Benpéridol; Benperidoli; Benperidolis; Benperidolum; Benzperidol; CB-8089; McN-JR-4584; R-4584; Бенперидол.

1-[1-[3-(4-Fluorobenzoyl)propyl]-4-piperidyl]benzimidazolin-2-one.

$C_{22}H_{24}FN_3O_2$=381.5

CAS — 2062-84-2.

ATC — N05AD07.

ATC Vet — QN05AD07.

UNII — 97O6X78C53.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Benperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Benperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). Doses of 0.25 to 1.5 mg daily in divided doses are given orally in the management of deviant sexual behaviour (below). Elderly or debilitated patients may require reduced doses and half the usual dose may be sufficient.

In some countries benperidol is given orally or parenterally for the treatment of psychotic conditions (p. 1030.2).

Deviant sexual behaviour. Results of a double-blind placebo-controlled crossover study found no difference between the effect of benperidol 1.25 mg daily, chlorpromazine 125 mg daily, or placebo on sexual drive and arousal in 12 paedophilic sexual offenders, except for a lower frequency of sexual thoughts with benperidol.[1] The effects of benperidol are unlikely to be sufficient to control severe forms of antisocial sexually deviant behaviour. The management of deviant sexual behaviour is discussed under Disturbed Behaviour on p. 1030.2.

1. Tennent G, *et al.* The control of deviant sexual behaviour by drugs: a double-blind controlled study of benperidol, chlorpromazine, and placebo. *Arch Sex Behav* 1974; 3: 261–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Prenactil; *Ger.*: Glianimon; *Gr.*: Glianimon; *Neth.*: Frenactil†; *UK*: Anquil.

Bentazepam *(USAN, rINN)*

Bentazépam; Bentazepamum; CI-718; QM-6008; Бентазепам.

1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*]-1,4-diazepin-2-one.

$C_{17}H_{16}N_2OS$=296.4

CAS — 29462-18-8.

UNII — 66JKK4351Z.

Profile

Bentazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given, in usual oral doses of 25 mg every 8 hours, in the short-term treatment of anxiety disorders (p. 1028.1); it has also been used in insomnia.

Effects on the liver. Severe chronic active hepatitis has been reported in a 65-year-old man who had received long-term treatment with bentazepam.[1]

1. Andrade RJ, *et al.* Bentazepam-associated chronic liver disease. *Lancet* 1994; 343: 860.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Tiadipona.

Blonanserin *(rINN)*

AD-5423; Blonanserina; Blonansérine; Blonanserinum; Блонансерин.

2-(4-Ethyl-1-piperazinyl)-4-(*p*-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclo-octa[*b*]pyridine.

$C_{23}H_{30}FN_3$=367.5

CAS — 132810-10-7.

UNII — AQ316B4F8C.

Profile

Blonanserin is an atypical antipsychotic reported to be an antagonist at dopamine D_2 and serotonin ($5\text{-}HT_2$) receptors. It is given orally for the treatment of schizophrenia (p. 1031.3) in an initial dose of 4 mg twice daily, increased gradually according to response thereafter. The usual maintenance dose is 8 to 16 mg daily; the maximum daily dose is 24 mg.

References.

1. Garcia E, *et al.* The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia: a randomized, double-blind, placebo-controlled, multicentre study. *CNS Drugs* 2009; 23: 615–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Lonasen.

Bromazepam *(BAN, USAN, rINN)*

Bromatsepaami; Brómazepám; Bromazépam; Bromazepamas; Bromazepamum; Ro-5-3350; Бромазепам.

7-Bromo-1,3-dihydro-5-(2-pyridyl)-1,4-benzodiazepin-2-one.

$C_{14}H_{10}BrN_3O$=316.2

CAS — 1812-30-2.

ATC — N05BA08.

ATC Vet — QN05BA08.

UNII — X015L14V0O.

NOTE. The name Seniran has been used as a trade mark for bromazepam.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bromazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble or sparingly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Bromazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been used in the short-term treatment of anxiety disorders (p. 1028.1) occurring alone or associated with insomnia. A usual initial oral dose for anxiety is 6 to 18 mg daily in divided doses. Doses up to 60 mg daily have occasionally been given. Initial doses for elderly and debilitated patients should not exceed 3 mg daily in divided doses.

References.

1. Kaplan SA, *et al.* Biopharmaceutical and clinical pharmacokinetic profile of bromazepam. *J Pharmacokinet Biopharm* 1976; 4: 1–16.
2. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; 41: 562–70.
3. Erb T, *et al.* Preoperative anxiolysis with minimal sedation in elderly patients: bromazepam or clorazepate-dipotassium? *Acta Anaesthesiol Scand* 1998; 42: 97–101.
4. Lakhal K, *et al.* Protracted deep coma after bromazepam poisoning. *Int J Clin Pharmacol Ther* 2010; 48: 79–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Atemperator; Balamol†; Benedorm†; Bromatanil†; Butecam†; Creosedin; Equisedin; Estomina; Fabozepam; Finaten; Gasmol; Lexotanil; Neurozepam; Nulastres; Octanyl; Sipcar; Tritopam; *Austral.*: Lexotan; *Austria*: Lexotanil; *Belg.*: Bromatop; Bromidem; Dochromaze†; Lexotan; *Braz.*: Bromalex; Bromoxon; Fluxtar; Lexfast; Lexotan; Lezepan; Nervium†; Neurilan; Relaxil†; Somalium; Uni Bromazepax; *Canad.*: Lectopam; *Chile*: Lexotanil; Totasedan†; *Cz.*: Lexaurin; *Denm.*: Bromam; Lexotan; *Fr.*: Anxyrex†; Lexomil; Quietiline; *Ger.*: Bromazanil†; Bromazep†; Gityl; Lexostad†; Lexotanil; neo OPT†; Normoc†; *Gr.*: Anconevron; Evagelin; Lexotanil; Libronil-R; Notorium; Pascalium; *Hong Kong*: Akamon; Lexilium†; Lexotan; *Indon.*: Lexotan; Lexzepam; *Irl.*: Lexotan; *Israel*: Lenitin†; *Ital.*: Brixopan; Compendium; Lexotan; *Malaysia*: Akamon; Lexotan; *Mex.*: Hatmmony; Lexotan; Otedram; *Philipp.*: Lexotan; *Pol.*: Lexotan; Sedam; *Port.*: Bromalex; Lexotan; Ultramidol; *Rus.*: Lexotan (Лексотан); *S.Afr.*: Brazepam; Bromaze; Lexotan; *Singapore*: Lexotan; *Spain*: Lexatin; *Switz.*: Lexotanil; *Thai.*: Lexotan; *Venez.*: Lexotanil; Nervan.

Multi-ingredient Preparations. *Arg.*: Biorgan B; Colixane B; Debridat B; Eudon; Eumotil-T; Faradil Novo; Fenatrop-A†; Miopropan-T; Somasedan; Vegestabil Digest; Veralipral T; *Braz.*: Bromopirin; Sulpan; *Ital.*: Lexil.

Bromisoval *(rINN)*

Bromisovaali; Bromisovalerylurea; Bromisovalum; Bromovalerylurea; Bromsoval; Bromvaleryfurea; Bromvaletone; Bromylum; Бромизовал.

N-(2-Bromo-3-methylbutyryl)urea.

$C_6H_{11}BrN_2O_2$=223.1

CAS — 496-67-3.

ATC — N05CM03.

ATC Vet — QN05CM03.

UNII — 469GW8R486.

Pharmacopoeias. In *Jpn.*

Profile

Bromisoval has actions and uses similar to those of carbromal (p. 1044.1) but the use of bromides is generally deprecated.

References.

1. Wang Y-T, *et al.* Pseudohyperchloraemia due to bromvalerylurea abuse. *Nephrol Dial Transplant* 2005; 20: 1767–8.
2. Kowa H, *et al.* A case of acute bromvalerylurea intoxication: clinical course and alteration in serum bromvalerylurea concentration. *No To Shinkei* 2006; 58: 323–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Pol.*: Milocardin; *Rus.*: Pagluferal (Пагмоферал).

Bromperidol *(BAN, USAN, rINN)*

Bromiperidoli; Brómperidol; Brompéridol; Bromperidoli; Bromperidolis; Bromperidolum; R-11333; Бромперидол.

4-[4-(*p*-Bromophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

$C_{21}H_{23}BrFNO_2$=420.3

CAS — 10457-90-6.

ATC — N05AD06.

ATC Vet — QN05AD06.

UNII — LYH6F7122E.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bromperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

Bromperidol Decanoate *(BANM, USAN, rINNM)*

Brompéridol, décanoate de; Bromperidol, decanoato de; Bromperidoldecanoat; Brómperidol-dekanoát; Bromperidol-dekanoat; Bromperidol-dekanoát; Bromperidoli Decanoas; Bromperidolidekanoaatti; Bromperidolio dekanoatas; Decanoato de bromperidol; R-46541; Бромперидола Деканоат.

$C_{31}H_{41}BrFNO_3$=574.6

CAS — 75067-66-2.

UNII — 73LG72M4LV.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bromperidol Decanoate). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane. It melts at about 60 degrees. Store at a temperature below 25 degrees. Protect from light.

Profile

Bromperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given in the treatment of schizophrenia (p. 1042.1) and other psychoses (p. 1030.2). Some bromperidol preparations are prepared with the aid of lactic acid and may be stated to contain bromperidol lactate. However, doses are expressed in terms of the equivalent amount of bromperidol. A usual oral dose is 1 to 15 mg daily, although up to 50 mg daily has been given. Elderly patients may require reduced doses of bromperidol. Bromperidol has also been given by intramuscular or intravenous injection.

The long-acting decanoate ester may be used for patients requiring long-term therapy with bromperidol. Doses are expressed in terms of the base; bromperidol decanoate 68.4 mg is equivalent to about 50 mg of bromperidol. Doses equivalent to up to 300 mg of bromperidol every 4 weeks have been given by deep intramuscular injection.

References.
1. Benfield P, *et al.* Bromperidol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in psychoses. *Drugs* 1988; 35: 670–84.

Schizophrenia. A systematic review[1] suggested that depot bromperidol had *some* benefits in schizophrenia (p. 1031.3) but was less effective than depot haloperidol or fluphenazine.

1. Adams CE, *et al.* Depot bromperidol decanoate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bromodol; Erodium; *Belg.*: Impromen; *Ger.*: Impromen; Tesoprel†; *Gr.*: Bromodol; *Ital.*: Impromen; *Neth.*: Impromen; *Thai.*: Brofed†.

Brotizolam *(BAN, USAN, rINN)*

Brotitsolaami; Brotizolamum; Brotyzolam; We-941-BS; We-941; Бротизолам.

2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine.

$C_{15}H_{10}BrClN_4S$=393.7

CAS — 57801-81-7.

ATC — N05CD09.

ATC Vet — QN05CD09.

UNII — 5XZM1R3DKF.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Brotizolam). A white or yellowish powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble or slightly soluble in methyl alcohol.

Profile

Brotizolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given for the short-term (up to 2 weeks) management of insomnia (p. 1033.2) in usual oral doses of 250 micrograms at night. The suggested dose for elderly and debilitated patients is 125 micrograms.

Abuse. Reference to abuse of brotizolam in Germany and Hong Kong.[1]

1. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_856.pdf (accessed 28/07/09)

Pharmacokinetics. References.
1. Bechtel WD. Pharmacokinetics and metabolism of brotizolam in humans. *Br J Clin Pharmacol* 1983; 16: 279S–283S.
2. Jochemsen R, *et al.* Pharmacokinetics of brotizolam in healthy subjects following intravenous and oral administration. *Br J Clin Pharmacol* 1983; 16: 285S–290S.
3. Tokairin T, *et al.* Inhibition of the metabolism of brotizolam by erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in brotizolam metabolism. *Br J Clin Pharmacol* 2005; 60: 172–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Lendorm; *Belg.*: Lendormin; *Chile*: Dormex; Noctilan; *Ger.*: Lendormin; *Gr.*: Lendormin; *Hung.*: Lendormin; *Israel*: Bondormin; *Ital.*: Lendormin; Nimbisan†; *Jpn*: Lendormin; *Mex.*: Lindormin; *Neth.*: Lendormin; *Port.*: Lendormin; *S.Afr.*: Lendormin; *Spain*: Sintonal; *Venez.*: Lendormin.

Buspirone Hydrochloride

(BANM, USAN, rINNM)

Buspiron Hidroklorür; Buspirona, hidrocloruro de; Buspirone, chlorhydrate de; Buspironhydrochlorid; Buspiron-hydrochlorid; Buspironhydroklorid; Buspironi hydrochloridum; Buspironihydroklorīdi; Buspironu chlorowodorek; Hidrocloruro de buspirona; MJ-9022-1; Буспирона Гидрохлорид.

8-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride.

$C_{21}H_{31}N_5O_2$,HCl=422.0

CAS — 36505-84-7 (buspirone); 33386-08-2 (buspirone hydrochloride).

ATC — N05BE01.

ATC Vet — QN05BE01.

UNII — 207LT9J9OC.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Buspirone Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 36: (Buspirone Hydrochloride). A white crystalline powder. Very soluble in water; sparingly soluble in alcohol and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol; very slightly soluble in ethyl acetate; practically insoluble in hexanes. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Buspirone hydrochloride is an azaspirodecanedione (azapirone) anxiolytic. It is reported to be largely lacking in sedative, anticonvulsant, and muscle relaxant actions.

In the short-term management of anxiety disorders (below), buspirone hydrochloride is given in initial oral doses of 5 mg two or three times daily. The dose may be increased in steps of 5 mg at 2- to 3-day intervals, if required, to a usual range of 15 to 30 mg daily given in divided doses. The recommended maximum daily dose, to be given in divided doses, is 45 mg in the UK and 60 mg in the USA.

Dose adjustments of buspirone may be necessary in patients also taking potent inhibitors or inducers of the cytochrome P450 isoenzyme CYP3A4. See Interactions, p. 1043.2, for further details.

Action. Buspirone has dopaminergic, noradrenergic, and serotonin-modulating properties[1] and its anxiolytic effects appear to be related to its action on serotonin (5-hydroxytryptamine, 5-HT) neurotransmission. Buspirone, and the related drugs gepirone (p. 1076.3) and tandospirone (p. 1109.1), are partial agonists at 5-HT_{1A} receptors.[1,2] While such drugs may inhibit serotonin neurotransmission (most likely via 5-HT_{1A} autoreceptor stimulation), they may also have postsynaptic 5-HT_{1A} agonist activity and thus facilitate serotonin neurotransmission.[1] To complicate matters further, 5-HT_{1A} partial agonists have shown both anxiolytic and anxiogenic properties in *animal* models of anxiety. Clinical studies have, however, shown that buspirone is effective in the treatment of generalised anxiety (see below).

Clinical studies with buspirone and gepirone suggest that 5-HT_{1A} partial agonists may have an antidepressant effect (see Depression, below), possibly by downregulation of either 5-HT_{1A} or 5-HT_2 receptors or both.[1] There is some suggestion that buspirone has an anti-aggressive action in humans (see Disturbed Behaviour, below); it is unclear whether this is mediated via dopaminergic or serotonergic mechanisms.[1]

Buspirone also has characteristics of both a dopamine agonist and antagonist; this may result in stimulation of both growth hormone and prolactin secretion.[3]

1. Glitz DA, Pohl R. 5-HT_{1A} partial agonists: what is their future? *Drugs* 1991; 41: 11–18.
2. Marsden CA. The pharmacology of new anxiolytics acting on 5-HT neurones. *Postgrad Med J* 1990; 66 (suppl 2): S2–S6.
3. Meltzer HY, *et al.* The effect of buspirone on prolactin and growth hormone secretion in man. *Arch Gen Psychiatry* 1983; 40: 1099–1102.

Anxiety disorders. Buspirone has been shown to be as effective as the benzodiazepines in the short-term treatment of generalised anxiety disorder (p. 1028.1) and to be less likely to cause sedation or psychomotor and cognitive impairment. It also appears to have a lower propensity for interaction with alcohol and a lower risk of abuse and dependence. However, its usefulness may be limited by a relatively slow response to treatment, which may take up to 2 to 4 weeks to appear. Its efficacy may be reduced in patients who have recently taken benzodiazepines. It appears to be ineffective in panic disorder and convincing evidence of efficacy in other anxiety disorders is lacking.

References.
1. Deakin JFW. A review of clinical efficacy of 5-HT_{1A} agonists in anxiety and depression. *J Psychopharmacol* 1993; 7: 283–9.
2. Peckniold JC. A risk-benefit assessment of buspirone in the treatment of anxiety disorders. *Drug Safety* 1997; 16: 118–32.
3. Fulton B, Brogden RN. Buspirone: an updated review of its clinical pharmacology and therapeutic applications. *CNS Drugs* 1997; 7: 68–88.
4. Chessick CA, *et al.* Azapirones for generalized anxiety disorder. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/04/08).
5. Mokhber N, *et al.* Randomized, single-blind, trial of sertraline and buspirone for treatment of elderly patients with generalized anxiety disorder. *Psychiatry Clin Neurosci* 2010; 64: 128–33.

Bruxism. SSRI-induced bruxism has been successfully controlled by adjunctive therapy with buspirone[1,2] and the related drug tandospirone (p. 1109.1).[3] However, such use has been questioned by the authors of another report[4] who suggested reducing the dosage of the SSRI first before giving buspirone.

1. Romanelli F, *et al.* Possible paroxetine-induced bruxism. *Ann Pharmacother* 1996; 30: 1246–7.
2. Bostwick JM, Jaffee MS. Buspirone as an antidote to SSRI-induced bruxism in 4 cases. *J Clin Psychiatry* 1999; 60: 857–60.
3. Kishi Y. Paroxetine-induced bruxism effectively treated with tandospirone. *J Neuropsychiatr Clin Neurosci* 2007; 19: 90–1.
4. Ranjan S, *et al.* Antidepressant-induced bruxism: need for buspirone? *Int J Neuropsychopharmacol* 2006; 9: 485–7.

Cerebellar ataxias. In general, the management of cerebellar ataxias is mainly supportive. Although buspirone improved some symptoms of ataxia in a small preliminary study[1] of patients with cerebellar cortical activity, a more recent small study[2] found that it was not superior to placebo in patients with spinocerebellar ataxia.

1. Trouillas P, *et al.* Buspirone, a 5-hydroxytryptamine$_{1A}$ agonist, is active in cerebellar ataxia: results of a double-blind drug placebo study in patients with cerebellar cortical atrophy. *Arch Neurol* 1997; 54: 749–52.
2. Assadi M, *et al.* Treatment of spinocerebellar ataxia with buspirone. *J Neurol Sci* 2007; 260: 143–6.

Depression. Buspirone has been investigated for augmentation of therapy with antidepressants with serotonin reuptake inhibiting activity in patients with refractory depression (p. 398.1), but results have been variable.

References.
1. Fischer P, *et al.* Weak antidepressant response after buspirone augmentation of serotonin reuptake inhibitors in refractory severe depression. *Int Clin Psychopharmacol* 1998; 13: 83–6.
2. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol* 1998; 18: 465–9.
3. Landen M, *et al.* A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry* 1998; 59: 664–8.
4. Appelberg BG, *et al.* Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry* 2001; 62: 448–52.
5. Önder E, Tural Ü. Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. *J Affect Disord* 2003; 76: 223–7.
6. Trivedi MH, *et al.* STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006; 354: 1243–52.

Disturbed behaviour. Buspirone has been tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (p. 1030.2) but evidence of efficacy is limited. Nonetheless, in the management of dementia, some[1] consider that it might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant or unresponsive to antipsychotics.

1. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; 164 (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)

Extrapyramidal disorders. Although there have been reports[1,2] that buspirone may improve symptoms of drug-induced dyskinesia (p. 1049.2), drugs with dopaminergic actions have mostly exacerbated symptoms and there are a few reports of extrapyramidal disorders with buspirone (see under Adverse Effects, p. 1043.1).

1. Moss LE, *et al.* Buspirone in the treatment of tardive dyskinesia. *J Clin Psychopharmacol* 1993; 13: 204–9.
2. Bonifati V, *et al.* Buspirone in levodopa-induced dyskinesias. *Clin Neuropharmacol* 1994; 17: 73–82.

Substance dependence. *ALCOHOL* Despite an early study suggesting that buspirone could reduce alcohol craving in alcohol dependent patients, later studies[2-4] have overall failed to confirm that buspirone improves abstinence or reduces alcohol consumption. Some studies[4,5] have also found that buspirone may improve certain psychopathological symptoms in these patients, although others[2] have found no such benefit; a meta-analysis[6] of 5 studies favoured the former interpretation.

The management of alcohol withdrawal and abstinence is discussed on p. 1735.1.

1. Bruno F. Buspirone in the treatment of alcoholic patients. *Psychopathology* 1989; 22 (suppl 1): 49–59.
2. Malcolm R, *et al.* A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcohol Clin Exp Res* 1992; 16: 1007–13.
3. George DT, *et al.* Buspirone does not promote long term abstinence in alcoholics. *Clin Pharmacol Ther* 1995; 57: 161.
4. Malec E, *et al.* Buspirone in the treatment of alcohol dependence: a placebo-controlled trial. *Alcohol Clin Exp Res* 1996; 20: 307–12.
5. Kranzler HR, *et al.* Buspirone treatment of anxious alcoholics: a placebo controlled trial. *Arch Gen Psychiatry* 1994; 51: 720–31.
6. Malec TS, *et al.* Efficacy of buspirone in alcohol dependence: a review. *Alcohol Clin Exp Res* 1996; 20: 853–8.

CANNABIS. Buspirone has been investigated in the treatment of cannabis dependence; 2 small studies[1,2] have shown some positive results.

1. McRae AL, *et al.* Buspirone for treatment of marijuana dependence: pilot study. *Am J Addict* 2006; 15: 404.
2. McRae-Clark AL, *et al.* A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend* 2009; 105: 132–8.

NICOTINE. A systematic review[1] noted that buspirone has produced conflicting results in the management of smoking cessation (p. 2570.2); however, its possible benefit cannot be ruled out based on evidence available at that time.

1. Hughes JR, *et al.* Anxiolytics for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/01/09).

OPIOIDS. Buspirone has been investigated in the management of opioid withdrawal (p. 109.2) in dependen

patients; 2 small studies[1,2] have produced encouraging results.

1. Rose JS, *et al.* Effects of buspirone in withdrawal from opiates. *Am J Addict* 2003; 12: 253–9.
2. Buydens-Branchey L, *et al.* Efficacy of buspirone in the treatment of opioid withdrawal. *J Clin Psychopharmacol* 2005; 25: 230–6.

Dependence and Adverse Effects

If adverse effects occur with buspirone hydrochloride, they are usually at the start of treatment and generally subside with continued treatment or decreased dosage. Dizziness, nausea, headache, nervousness, light-headedness, and excitement are amongst the most frequent adverse effects reported. Other adverse effects have included tachycardia, palpitations, non-specific chest pain, drowsiness, paraesthesias, sleep disturbances, confusion, seizures, dry mouth, tinnitus, sore throat, nasal congestion, fatigue, and sweating. A syndrome of restlessness appearing shortly after the start of treatment has been reported in a small number of patients given buspirone. Buspirone is reported to produce less sedation, and to have a lower potential for abuse and dependence, than the benzodiazepines.

Effects on the nervous system. Mild acute hypertension and panic were reported on two occasions after the addition of single 10-mg doses of buspirone to therapy with tricyclic antidepressants in a 40-year-old man with panic disorder. Adrenergic or serotonin dysfunction were postulated as possible mechanisms for the reaction.[1,2] Psychotic reactions associated with buspirone treatment have also been reported in a few patients.[3] There have also been isolated reports of mania,[4] and seizures have been reported, mainly in overdosage.[5]

1. Chignon JM, Lepine JP. Panic and hypertension associated with single dose of buspirone. *Lancet* 1989; ii: 46–7.
2. Norman TR, Judd FK. Panic attacks, buspirone, and serotonin function. *Lancet* 1989; ii: 615.
3. Friedman R. Possible induction of psychosis by buspirone. *Am J Psychiatry* 1991; 148: 1606.
4. Price WA, Bielefeld M. Buspirone-induced mania. *J Clin Psychopharmacol* 1989; 9: 150–1.
5. Catalano G, *et al.* Seizures associated with buspirone overdose: case report and literature review. *Clin Neuropharmacol* 1998; 21: 347–50.

EXTRAPYRAMIDAL DISORDERS. There have been isolated reports of exacerbation or precipitation of movement disorders[1–4] associated with the use of buspirone. However, buspirone has also been reported to have been of benefit in some patients with tardive dyskinesia (see Extrapyramidal Disorders under Uses and Administration, p. 1042.3).

1. Hammerstad JP, *et al.* Buspirone in Parkinson's disease. *Clin Neuropharmacol* 1986; 9: 556–60.
2. Ritchie EC, *et al.* Acute generalized myoclonus following buspirone administration. *J Clin Psychiatry* 1988; 49: 242–3.
3. Strauss A. Oral dyskinesia associated with buspirone use in an elderly woman. *J Clin Psychiatry* 1988; 49: 322–3.
4. LeWitt PA, *et al.* Persistent movement disorders induced by buspirone. *Mov Disord* 1993; 8: 331–4.

Precautions

Buspirone hydrochloride should be used with caution in patients with renal or hepatic impairment and is contra-indicated if the impairment is severe. It should not be used in patients with epilepsy or a history of such disorders. It does not show cross-tolerance with benzodiazepines or other common sedatives or hypnotics and will not block symptoms of their withdrawal; they should, therefore, be gradually withdrawn before starting treatment with buspirone. Buspirone may impair the patient's ability to drive or operate machinery.

Diagnosis and testing. Buspirone may interfere with diagnostic assays of urinary catecholamines.[1]

1. Cook FJ, *et al.* Effect of buspirone on urinary catecholamine assays. *N Engl J Med* 1995; 332: 401.

Hepatic impairment. Caution has been advised when using buspirone in patients with liver disease. The mean peak plasma-buspirone concentration after an oral dose was about 16 times higher in cirrhotic patients than in controls[1] and the elimination half-life was prolonged about twofold. A secondary peak concentration was seen in some subjects, occurring between 4 and 24 hours after a dose in the cirrhotics and after between 2 and 8 hours in controls. Data from a multiple-dose study[2] suggested that there was accumulation of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine in hepatic impairment, but that plasma concentrations appeared to reach steady state after 3 days regardless of the state of liver function. The AUC and mean peak concentration for buspirone were both higher in patients with hepatic impairment than in healthy subjects, but there were no significant differences for its metabolites. Specific dosing recommendations could not be made for patients with hepatic impairment because of the high intra- and inter-subject variations in plasma-buspirone concentrations.

1. Dalhoff K, *et al.* Buspirone pharmacokinetics in patients with cirrhosis. *Br J Clin Pharmacol* 1987; 24: 547–50.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; 46: 41–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies buspirone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/07/11)

Pregnancy and breast feeding. In some *animal* studies, large doses of buspirone during pregnancy had adverse effects on survival and on birth and weanling weight. Distribution into milk has been found in studies in *rats*. Recommendations in licensed product information for use during pregnancy or breast feeding vary from avoid, if possible, to contra-indicated.

Renal impairment. Caution has been advised when giving buspirone to patients with renal impairment.[1,2] There is evidence of accumulation of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine after repeated doses but plasma concentrations appeared to reach steady state after 3 days regardless of the degree of renal function. At steady state both the AUC and maximum concentrations for buspirone and its metabolite were greater in patients with renal failure than in healthy subjects. The metabolite, but not the parent drug, was removed by haemodialysis. Specific dosing recommendations could not be made for patients with renal impairment because of the high intra- and inter-subject variations in buspirone plasma concentrations on repeated dosage.

1. Caccia S, *et al.* Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. *Clin Pharmacokinet* 1988; 14: 171–7.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; 46: 41–7.

Interactions

The sedative effects of buspirone may be enhanced if taken with alcohol or other CNS depressants. Because of reports of increased blood pressure in patients receiving buspirone hydrochloride with an MAOI, licensed product information for buspirone recommends that it should not be given with an MAOI.

The metabolism of buspirone is mediated by the cytochrome P450 isoenzyme CYP3A4 and therefore there is the potential for interactions between buspirone and other drugs that inhibit, induce, or act as a substrate for this isoenzyme. The dose of buspirone may need to be reduced if given at the same time as potent inhibitors of CYP3A4 such as diltiazem, erythromycin, itraconazole, nefazodone, ritonavir, and verapamil; licensed product information suggests giving 2.5 mg of buspirone orally once or twice daily when used with such drugs. Grapefruit juice may also increase plasma concentrations of buspirone and should be avoided. Conversely, plasma concentrations of buspirone may be reduced by enzyme-inducing drugs such as rifampicin and the dosage of buspirone may need adjusting with such use.

Antidepressants. Serotonin syndrome (p. 443.2) has been reported with the use of buspirone with *citalopram*,[1] with *fluoxetine*,[2] and with *St John's wort*.[3]

1. Spigset O, Adielsson G. Combined serotonin syndrome and hyponatraemia caused by a citalopram-buspirone interaction. *Int Clin Psychopharmacol* 1997; 12: 61–3.
2. Manos GH. Possible serotonin syndrome associated with buspirone added to fluoxetine. *Ann Pharmacother* 2000; 34: 871–4.
3. Dannawi M. Possible serotonin syndrome after combination of buspirone and St John's Wort. *J Psychopharmacol* 2002; 16: 401.

Antipsychotics. For the effect of buspirone on serum concentrations of *haloperidol*, see under Chlorpromazine, p. 1053.1. For a report of potentially fatal gastrointestinal bleeding and marked hyperglycaemia after use of buspirone with *clozapine*, see under Clozapine, p. 1062.1.

Antivirals. Parkinson-like symptoms developed in a 54-year-old man taking a drug regimen that included buspirone, *indinavir*, and *ritonavir*.[1] It was suspected that ritonavir, a more potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 than indinavir, was mainly responsible for causing increased plasma-buspirone concentrations. Symptoms resolved after a change in antiviral regimen and reduction in the dose of buspirone.

1. Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. *Ann Pharmacother* 2003; 37: 202–5.

Pharmacokinetics

Buspirone hydrochloride is rapidly absorbed from the gastrointestinal tract reaching peak plasma concentrations within 40 to 90 minutes after an oral dose. Systemic bioavailability is low because of extensive first-pass metabolism, but may be increased if given with food as this delays absorption from the gastrointestinal tract and thereby reduces presystemic clearance. Buspirone is about 95% bound to plasma proteins. Metabolism in the liver is extensive via the cytochrome P450 isoenzyme CYP3A4; hydroxylation yields several inactive metabolites and oxidative dealkylation produces 1-(2-pyrimidinyl)-piperazine, which is reported to be about 25% as potent as the parent drug in one model of anxiolytic activity. The elimination half-life of buspirone is usually about 2 to 4 hours but half-lives of up to 11 hours have been reported. Buspirone is excreted mainly as metabolites in the urine, and also in the faeces. Distribution of buspirone and its metabolites into milk has been found in studies in *rats*.

References.
1. Mahmood I, Sabajwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet* 1999; 36: 277–87.
2. Edwards DJ, *et al.* Pharmacokinetics of buspirone in autistic children. *J Clin Pharmacol* 2006; 46: 508–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ansial; Aristopiron†; *Austral.*: Buspar; *Austria*: Buspar; *Belg.*: Buspar†; *Braz.*: Ansitec; Buspar; *Canad.*: Buspar†; Bustab; *Chile*: Paxon; *China*: Qibite (奇比特); Suxin (苏新); Yi Shu (一舒); *Denm.*: Buspar†; *Fin.*: Anksilon; Buspar†; *Fr.*: Buspar†; *Ger.*: Anxut; Bespar†; Buspi†; *Gr.*: Abivax; Anchocalm; Antipsichos; Bergamol; Bespar; Boronex; Epsilat; Hiremon; Hobatstress; Komasin; Lanamont; Lebilon; Ledion; Lostress; Loxapin; Nadrifor; Nervostal; Nevrorestol; Norbal; Pendium; Stressigal; Svitalark; Tendan; Tensispes; Trafuril; Umolit; Vulbefer; *Hong Kong*: Buspar†; Kalmiren†; *Hung.*: Anxiron; Spitomin; *India*: Buscalm; Buson; Buspidac; Buspin; *Indon.*: Tran-Q†; Xiety; *Irl.*: Buspar†; *Israel*: Sorbon; *Ital.*: Buspar†; *Mex.*: Buspar; *Norw.*: Buspar†; *NZ*: Biron; Buspar; *Pol.*: Mabuson†; Spamilan; *Port.*: Ansiten; Busansil; Buscalma; Buspar†; Buspium†; Itagil; Psibeter†; *Rus.*: Spitomin (Спитомин); *S.Afr.*: Buspar; Pasrin; *Spain*: Buspar†; *Swed.*: Buspar†; *Switz.*: Buspar†; *Thai.*: Anxiolan; *Turk.*: Buspon; *UK*: Buspar†; *USA*: Buspar†; *Venez.*: Dalpas.

Pharmacopoeial Preparations
USP 36: Buspirone Hydrochloride Tablets.

Butalbital *(USAN, rINN)*

Alisobumalum; Allylbarbital; Allylbarbituric Acid; Butalbitaali; Butalbitalum; Itobarbital; Tetrallobarbital; Буталбитал.

5-Allyl-5-isobutylbarbituric acid.

$C_{11}H_{16}N_2O_3$=224.3

CAS — 77-26-9.

UNII — KHSOAZ4JVK

NOTE. The name Butalbital has also been applied to talbutal, the *S*-butyl analogue, which was formerly used as a hypnotic and sedative.

Compounded preparations of butalbital may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine

Pharmacopoeias. In *US*.

USP 36: (Butalbital). A white odourless crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in alcohol, in chloroform, and in ether; soluble in solutions of fixed alkalis and alkali carbonates. A saturated solution is acid to litmus.

Profile

Butalbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used mainly in combination preparations with analgesics in the treatment of occasional tension-type headaches, but other treatments are generally preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Fiorinal C; Fiorinal; Pronal-C; Pronal; ratio-Tecnal C; ratio-Tecnal; Trianal C; Trianal; *Ital.*: Optalidon; *Switz.*: Cafergot-PB†; *USA*: Alagesic LQ; Amaphen with Codeine; Americet; Anolor; Ascomp with Codeine; Bupap; Butex; Capacet; Cephadyn; Dolgic LQ; Dolgic Plus; Dolgic; Endolor; Esgic-Plus; Esgic; Floricet with Codeine; Floricet; Fiorinal with Codeine; Fiorinal; Margesic; Marten-Tab; Medigesic†; Orbivan CF; Orbivan; Pacaps; PhenazoForte Plus; Phrenilin w Caffeine and Codeine; Phrenilin; Promacet; Prominol; Pyridium Plus; Repan; Sedapap; Tencet; Tencon; Trellium Plus†; Triad; Zebutal.

Pharmacopoeial Preparations
USP 36: Butalbital and Aspirin Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules.

Butobarbital *(BAN)*

Butethal; Butobarbitaali; Butobarbitalum; Butobarbitone; Бутобарбитал.
5-Butyl-5-ethylbarbituric acid.
$C_{10}H_{16}N_2O_3$=212.2
CAS — 77-28-1.
ATC — N05CA03.
ATC Vet — QN05CA03.
UNII — OHZ8QAW6YC.

NOTE. Care should be taken to avoid confusion between barbiturates with similar names: Butobarbital should be distinguished from Butabarbital, a synonym for Secbutabarbital (p. 1106.2), and Secbutabarbital should be distinguished from Secobarbital (p. 1106.3).

Profile

Butobarbital is a barbiturate that has been used as a hypnotic. It has general properties similar to those of amobarbital (p. 1037.2). Its use can no longer be recommended because of the risk of its adverse effects and of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p. 1033.2) in patients already taking it. It was given in usual oral doses of 100 to 200 mg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Soneryl.

Calcium Bromolactobionate

Bromolactobionato de calcio; Calcium Galactogluconate Bromide.
Calcium bromide lactobionate hexahydrate.
$Ca(C_{12}H_{21}O_{12})_2CaBr_2.6H_2O$=1062.6
CAS — 33659-28-8 (anhydrous calcium bromolactobionate).
UNII — 46EGF47S9V.

Profile

Calcium bromolactobionate has sedative properties and has been given orally in the treatment of insomnia and anxiety disorders. The use of bromides is generally deprecated.

Overdosage. Bromide intoxication has been reported[1] in a patient after overdosage with calcium bromolactobionate tablets.

1. Daniel VC, *et al.* Bromide intoxication and pseudohyperchloremia. *Ann Pharmacother* 2001; 35: 386–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Bromocalcio†; Nervoltat†; Sedofantil; *Ital.*: Calcibronat; *Mon.*: Calcibronat.

Captodiame Hydrochloride *(BANM, pINNM)*

Captodiame, Chlorhydrate de; Captodiami Hydrochloridum; Captodiamine Hidrochloride; Captodiamine Hydrochloride; Captodiamo, hidrocloruro de; Hidrocloruro de captodiamo; Каптодиама Гидрохлорид.
2-(4-Butylthiobenzhydrylthio)ethyldimethylamine hydrochloride.
$C_{21}H_{29}NS_2.HCl$=396.0
CAS — 486-17-9 (captodiame); 904-04-1 (captodiame hydrochloride).
ATC — N05BB02.
ATC Vet — QN05BB02.
UNII — 9I7N9PR9J2.

Profile

Captodiame hydrochloride is given in oral doses of 50 mg three times daily for the treatment of anxiety disorders (p. 1028.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Covatine.

Carbromal *(BAN, rINN)*

Bromodiethylacetylurea; Carbromalum; Karbromaali; Karbromal; Карбромал.
N-(2-Bromo-2-ethylbutyryl)urea.
$C_7H_{13}BrN_2O_2$=237.1
CAS — 77-65-6.
ATC — N05CM04.
ATC Vet — QN05CM04.
UNII — 0Y299JY9V3.

Profile

Carbromal is a bromureide with general properties similar to those of the barbiturates (see Amobarbital, p. 1037.2). It was formerly used for its hypnotic and sedative properties. Chronic use of carbromal could result in bromide accumulation and symptoms resembling bromism (see Bromides, p. 2461.1). The use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Demalgon.

Carpipramine Hydrochloride *(rINNM)*

Carpipramina, hidrocloruro de; Carpipramine, Chlorhydrate de; Carpipramine Dihydrochloride; Carpipramini Hydrochloridum; Hidrocloruro de carpipramina; PZ-1511; Карпипрамина Гидрохлорид.
1-[3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl]-4-piperidinopiperidine-4-carboxamide dihydrochloride monohydrate.
$C_{28}H_{38}N_4O.2HCl.H_2O$=537.6
CAS — 5942-95-0 (carpipramine); 7075-03-8 (anhydrous carpipramine hydrochloride); 100482-23-3 (carpipramine maleate).
UNII — 53X71X3I1W.

Profile

Carpipramine is structurally related both to imipramine (p. 426.2) and to butyrophenones such as haloperidol (p. 1077.1). It has been used in the management of anxiety disorders (p. 1028.1) and psychoses such as schizophrenia (p. 1031.3). Carpipramine is given as the hydrochloride although doses are expressed in terms of the base; carpipramine hydrochloride 60.2 mg is equivalent to about 50 mg of carpipramine. A usual oral dose is equivalent to 150 mg of the base daily in 2 or 3 divided doses, with a range of 50 to 400 mg daily. The maleate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Prazinil; *Jpn*: Defekton.

Chlordiazepoxide *(BAN, rINN)*

Chlordiazepoksidas; Chlordiazepoxid; Chlordiazépoxide; Chlordiazepoxidum; Chlorodiazepoksyd; Clordiazepóssido; Clordiazepóxido; Klooridiatsepoksidi; Klordiazepoksit; Klordiazepoxid; Klórdiazepoxid; Methaminodiazepoxide; Хлордиазепоксид.
7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide.
$C_{16}H_{14}ClN_3O$=299.8
CAS — 58-25-3.
ATC — N05BA02.
ATC Vet — QN05BA02.
UNII — 6RZ6XEZ3CR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of chlordiazepoxide:

Green apples; Green and blacks; Lib.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Chlordiazepoxide). An almost white or light yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Chlordiazepoxide). A yellow, practically odourless, crystalline powder. Insoluble in water; soluble 1 in 50 of alcohol, 1 in 6250 of chloroform, and 1 in 130 of ether. Store in airtight containers. Protect from light.

Chlordiazepoxide Hydrochloride

(BANM, USAN, rINNM)

Chlordiazepoksido hidrochloridas; Chlordiazepoksydu chlorowodorek; Chlordiazépoxide, chlorhydrate de; Chlordiazepoxidhydrochlorid; Chlordiazepoxid-hydrochlorid; Chlordiazepoxidi Hydrochloridum; Clordiazepóxido, hidrocloruro de; Hidrocloruro de clordiazepóxido; Klooridiatsepoksidihüdrokloriid; Klordiazepoksit Hidroklorür; Klórdiazepoxid-hidroklorid; Klordiazepoxidhydroklorid; Methaminodiazepoxide Hydrochloride; NSC-115748; Ro-5-0690; Хлордиазепоксида Гидрохлорид.
$C_{16}H_{14}ClN_3O.HCl$=336.2
CAS — 438-41-5.
ATC — N05BA02.
ATC Vet — QN05BA02.
UNII — MFM6K1XWDK.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Chlordiazepoxide Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Chlordiazepoxide Hydrochloride). A white or practically white, odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; insoluble in petroleum spirit. Store in airtight containers. Protect from light.

Uses and Administration

Chlordiazepoxide is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.). It is used in the short-term treatment of anxiety disorders (p. 1028.1) occurring alone or associated with insomnia. Chlordiazepoxide is also used in muscle spasm (p. 2014.1) and in alcohol withdrawal syndrome (p. 1735.1); it has been given for premedication.

Chlordiazepoxide is given orally as the hydrochloride or the base; the doses given apply equally to both. It has also been given by deep intramuscular or slow intravenous injection as the hydrochloride.

Elderly and debilitated patients should be given one-half or less of the usual dose.

The usual oral dose for the treatment of **anxiety** is up to 30 mg daily in divided doses; in severe conditions up to 100 mg daily has been given. For insomnia associated with anxiety, 10 to 30 mg may be given orally before bedtime. Oral doses of 5 to 10 mg may be given 3 or 4 times daily on the days preceding surgery for pre-operative apprehension and anxiety.

For relief of **muscle spasm** a dose of 10 to 30 mg daily given orally in divided doses is recommended.

For the control of the acute symptoms of **alcohol withdrawal** chlordiazepoxide or chlordiazepoxide hydrochloride may be given in an oral dose of 25 to 100 mg repeated as needed after 2 to 4 hours, up to a maximum of 300 mg daily.

For details of doses in children, see below.

Administration in children. In the USA, chlordiazepoxide hydrochloride is licensed for use in children aged 6 years or over for the short-term treatment of anxiety disorders and for pre-operative apprehension and anxiety. An oral dose of 5 mg may be given 2 to 4 times daily; in some children this may be increased to 10 mg 2 or 3 times daily.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 12.5 mg of chlordiazepoxide is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Hepatic impairment. Progressive drowsiness began after 20 days of treatment with chlordiazepoxide in a woman with cirrhosis and hepatitis.[1] One week after stopping the drug the patient could not be roused, and full consciousness was not regained for another week. Accumulation of active metabolites of chlordiazepoxide may have been responsible for the prolonged stupor.

1. Barton K, *et al.* Chlordiazepoxide metabolite accumulation in liver disease. *Med Toxicol* 1989; 4: 73–6.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Absorption of chlordiazepoxide is almost complete after oral doses; peak plasma concentrations occur after 1 to 2 hours. Absorption after intramuscular injection may be slow and erratic depending on the site of injection. Chlordiazepoxide is about 96% bound to plasma proteins. Reported values for the elimination half-life of chlordiazepoxide have ranged from about 5 to 30 hours, but its main active metabolite desmethyldiazepam (nordazepam, p. 1089.3) has a half-life of several days. Other pharmacologically active metabolites of chlordiazepoxide include desmethylchlordiazepoxide, demoxepam, and oxazepam (p. 1092.2). Chlordiazepoxide passes into the CSF and breast milk, and crosses the

placenta. Unchanged drug and metabolites are excreted in the urine, mainly as conjugated metabolites.

References.
1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of chlordiazepoxide. *Clin Pharmacokinet* 1978; 3: 381–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: OCM; *Braz.*: Psicosedin; *Cz.*: Elenium; *Denm.*: Klopoxid: Risolid†; *Fin.*: Risolid; *Ger.*: Librium; Multum†; Radepur; *Gr.*: Oasil; *Hong Kong*: Corlium†; Librium; Litamin; *Hung.*: Elenium; Librium; *India*: Anxizide; Cebrum: Cloxide; Ebrium; Equilibrium; Lib-CT; Librium; *Indon.*: Cetabrium†; Librium; *Irl.*: Librium; Rima†; *Ital.*: Librium; *Malaysia*: Benpine; *NZ*: Novapam; *Pol.*: Elenium; *Port.*: Paxium; *Rus.*: Elenium (Элениум); *S.Afr.*: Librium†; *Singapore*: Benpine; Klorpo; *Spain*: Huberplex; Omnalio†; *Thai.*: Benpine; Chlordibrax; Chlordixide; Chlorzep; Comoben; Cozep; Epoxide; Med-Zepoxide; Metaxide; Minoxide; Zepoxide; Zepoxin; *UK*: Librium; Tropium; *USA*: Librium; *Venez.*: Eposal.

Multi-ingredient Preparations. *Arg.*: Libraxin; *Austria*: Limbitrol; *Braz.*: Limbitrol; Menotensil; *Canad.*: Apo-Chlorax; Librax; Pro Chlorax†; *Chile*: Aero Itan; Aerogastrol; Antalin; Garceptol; Gastrolen; Lerogin; Libraxin; Limbatrilin; Morelin; No-Ref; Profisin; Tensoliv; Tiperin; *China*: Fufang Dan An Pian (复方胆氨片); *Fin.*: Klotriptyl; Librax; Limbitrol; *Fr.*: Librax; *Gr.*: Librax; Pro-Alusin-L; *Hong Kong*: Epilon; Librax; Syntabrax†; *India*: Acirex; Alspas Forte; Amichlor; Amixide H; Amize; Amizep; Amrea-C; Amypres-C; Anxitab; Cebrex Forte; Cebrex; Chlotrip; Cibis; Clidox; Cloxide Plus; Colinorm; Cynosleep; Depsodep; Dorpep; Emotrip; Equicalm; Equirex; Febl; Fit; Gentrip Forte; Gentrip Plus; IBS; Libotryp; Librax; Librodep; Librospas; Librosym; Librotop; Limbitrol; Limbival; Meva-C; Mirip; Mitryp; Neurospas-CD; Normaline Plus; Normaline-H; Normaxin-RT; Normaxin; Normozin; Orlidox-D; Orlidox; Parazin-C; Spasrax; *Indon.*: Braxidin; Cliad; Klidibrax; Librax; Limbitrol; Melidox; Neurogen†; Renagas; Sanmag; Spasmium; *Israel*: Nirvaxal†; *Ital.*: Diapatol; Librax; Limbitryl; Sedans; *Malaysia*: Liblan; *Port.*: Librax; *Rus.*: Amixide (Аминсид); *S.Afr.*: Librax†; Limbitrol†; *Singapore*: Apo-Chlorax; Chlobax; Librax†; Medocalum†; Syntabrax; *Spain*: Psico Blocan†; *Switz.*: Librax; Librocol; Limbitrol; *Thai.*: Cebarax†; Dirax; Kenspa; Librax; Licon; Modurax; Pobrax; Radlbrax; Tumax; Utorax; *Turk.*: Klipaks; Libkol; Librax; *USA*: Clindex; Librax; Limbitrol; *Venez.*: Librax.

Pharmacopoeial Preparations
BP 2014: Chlordiazepoxide Capsules; Chlordiazepoxide Hydrochloride Tablets;
USP 36: Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules; Chlordiazepoxide Hydrochloride Capsules; Chlordiazepoxide Hydrochloride for Injection; Chlordiazepoxide Tablets.

Chlormezanone *(BAN, rINN)*

Chlormethazanone; Chlormézanone; Chlormezanonum; Clormezanona; Kloorimetsanoni; Klormezanon; Хлормезанон.

2-(4-Chlorophenyl)-3-methylperhydro-1,3-thiazin-4-one 1,1-dioxide.

$C_{11}H_{12}ClNO_3S$=273.7

CAS — 80-77-3.

ATC — M03BB02.

ATC Vet — QM03BB02.

UNII — GP568V9G19.

Profile

Chlormezanone has been used in the treatment of anxiety disorders and insomnia. It was also used in conditions associated with painful muscle spasm, often in compound preparations with analgesics; its mechanism of action is not clear but is probably related to its sedative effect. Chlormezanone was withdrawn from use in many countries after reports of serious skin reactions (see below).

Effects on the skin. Chlormezanone was responsible for 5 of 86 cases of fixed drug eruption detected in a Finnish hospital from 1971 to 1980.[1] In the period from 1981 to 1985 chlormezanone was responsible for 1 out of 77 such eruptions.[2] In a case control study[3] comparing drug use in 245 patients hospitalised because of toxic epidermal necrolysis or Stevens-Johnson syndrome and 1147 controls, 13 patients and one control were found to have taken chlormezanone. From these figures a high crude relative risk of 62 was calculated; the excess risk was estimated to be 1.7 cases per million users per week.

1. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Dermatol* 1985; 112: 575–8.
2. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; 120: 583.
3. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; 333: 1600–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Ansioval; Calmosedan; Cardiosedantol; Diapam; Dolnix; Dolonase; Fibrorelax; Multisedil; Neo Butartrol; Precenid; Promidan; Sedantol; Sedilit; Sin-Algin; *Hong Kong*: Parazone; *India*: Dilofen-MR; Dolobak; Ontact Forte; *S.Afr.*: Myoflex†.

Chlorpromazine *(BAN, rINN)*

Chlorpromazinum; Clorpromazina; Klooripromatsiini; Klorpromazin; Хлорпромазин.

3-(2-Chlorophenothiazin-10-yl)propyldimethylamine.

$C_{17}H_{19}ClN_2S$=318.9

CAS — 50-53-3.

ATC — N05AA01.

ATC Vet — QN05AA01.

UNII — U42B7VYA4P.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Chlorpromazine). A white or creamy-white powder or waxy solid; odourless or almost odourless. M.p. 56 degrees to 58 degrees. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform. Protect from light.

USP 36: (Chlorpromazine). A white crystalline solid with an amine-like odour. It darkens on prolonged exposure to light. Practically insoluble in water; soluble 1 in 3 of alcohol, 1 in 2 of chloroform, 1 in 3 of ether, and 1 in 2 of benzene; freely soluble in dilute mineral acids; practically insoluble in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Chlorpromazine Embonate *(BANM, rINNM)*

Chlorpromazine, Embonate de; Chlorpromazine Pamoate; Chlorpromazini Embonas; Clorpromazina, embonato de; Embonato de clorpromazina; Хлорпромазина Эмбонат.

$(C_{17}H_{19}ClN_2S)_2.C_{23}H_{16}O_6$=1026.1

ATC — N05AA01.

ATC Vet — QN05AA01.

UNII — 85RG9X8ZHE.

Chlorpromazine Hydrochloride

(BANM, rINNM)

Aminazine; Chloropromazyny chlorowodorek; Chlorpromazin hydrochlorid; Chlorpromazine, Chlorhydrate de; Chlorpromazinhydrochlorid; Chlorpromazini Hydrochloridum; Chlorpromazino hidrochloridas; Clorpromazina, hidrocloruro de; Hidrocloruro de clorpromazina; Klooripromatsiinihydrokloridi; Klorpromazin Hidroklorür; Klórpromazín-hidroklorid; Klorpromazinhydroklorid; Хлорпромазина гидрохлорид.

$C_{17}H_{19}ClN_2S.HCl$=355.3

CAS — 69-09-0.

ATC — N05AA01.

ATC Vet — QN05AA01.

UNII — 9WP59609J6.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chlorpromazine Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. It decomposes on exposure to air and light. Very soluble in water; freely soluble in alcohol. A freshly prepared 10% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Chlorpromazine Hydrochloride). A white or slightly creamy-white odourless crystalline powder. It darkens on prolonged exposure to light. Soluble 1 in 1 of water, 1 in 1.5 of alcohol, and 1 in 1.5 of chloroform; insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Dilution. Solutions containing 2.5% of chlorpromazine hydrochloride may be diluted to 100 mL with 0.9% sodium chloride solution provided that the pH of the dilution does not exceed the critical range of pH 6.7 to 6.8.[1] Using saline of pH 7.0 or 7.2, the final solution had a pH of 6.4.

1. D'Arcy PF, Thompson KM. Stability of chlorpromazine hydrochloride added to intravenous infusion fluids. *Pharm J* 1973; 210: 28.

Incompatibility. Incompatibility has been reported between chlorpromazine hydrochloride injection and several other compounds; precipitation of chlorpromazine base from solution is particularly likely if the final pH is increased. Compounds reported to be incompatible with chlorpromazine hydrochloride include aminophylline, amphotericin B, aztreonam, some barbiturates, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, morphine sulfate (when preserved with chlorocresol), some penicillins, and remifentanil.

For a warning about incompatibility between chlorpromazine solution (*Thorazine; GSK, USA*) and carbamazepine suspension (*Tegretol; Novartis, USA*), see p. 512.2.

Sorption. There was a 41% loss of chlorpromazine hydrochloride from solution when infused for 7 hours via a plastic infusion set (cellulose propionate burette with PVC tubing), and a 79% loss after infusion for 1 hour from a glass syringe through silastic tubing.[1] Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; 39: 460–7.

Uses and Administration

Chlorpromazine is a phenothiazine antipsychotic. It has a wide range of activity arising from its depressant actions on the CNS and its alpha-adrenergic blocking and antimuscarinic activities. Chlorpromazine is a dopamine inhibitor; the turnover of dopamine in the brain is also increased. There is some evidence that the antagonism of central dopaminergic function, especially at the D_2-dopaminergic receptor, is related to therapeutic effect in psychotic conditions. Chlorpromazine possesses sedative properties but patients usually develop tolerance rapidly to the sedation. It has antiemetic, serotonin-blocking, and weak antihistaminic properties and slight ganglion-blocking activity. It inhibits the heat-regulating centre so that the patient tends to acquire the temperature of the surroundings (poikilothermy). Chlorpromazine can relax skeletal muscle.

Chlorpromazine is widely used in the management of psychotic conditions as well as in some non-psychotic disorders, such as:

- acute and chronic schizophrenia (p. 1047.1)
- to reduce acute mania, as in bipolar disorder (p. 1046.2)
- control of severely disturbed, agitated, or violent behaviour (p. 1030.2) and sometimes other psychiatric conditions
- as an adjunct for the short-term treatment of severe anxiety (but see also p. 1028.1), and to reduce preoperative anxiety
- as an antiemetic in some forms of nausea and vomiting (p. 1047.1); it is ineffective in motion sickness
- in the alleviation of intractable hiccup (p. 1046.3)
- as an adjunct in the treatment of tetanus (p. 209.2 and p. 2029.2) and to control symptoms in acute intermittent porphyria (p. 1556.1)
- for induction of hypothermia

Chlorpromazine is given orally as the hydrochloride and the embonate. For both salts, the doses are expressed as the hydrochloride; chlorpromazine embonate 144 mg is equivalent to about 100 mg of chlorpromazine hydrochloride. The phenolphthalinate has also been used orally. Chlorpromazine is also given by injection as the hydrochloride and doses are expressed in terms of this salt. The base is given rectally as suppositories; doses are in terms of the base.

Dosage varies both with the individual and with the purpose for which the drug is being used. In most patients with **psychiatric conditions** *oral treatment* may be used from the start, typically commencing with a dosage of 25 mg of the hydrochloride, or its equivalent as the embonate, three times daily and increasing as necessary; daily doses of 75 mg may be given as a single dose at night. In some patients doses of 10 mg three times daily may be adequate. Maintenance doses, when required, usually range from 25 to 100 mg three times daily, although psychotic patients may require daily doses of up to 1 g or more.

For *parenteral use*, deep intramuscular injection is preferable for psychiatric and most **other indications**, but diluted solutions have sometimes been given by slow intravenous infusion for indications such as tetanus, severe intractable hiccup, or nausea and vomiting associated with surgery. Subcutaneous injection is contra-indicated. After injection of chlorpromazine, patients should remain in the supine position for at least 30 minutes; blood pressure should be monitored. The usual dose by intramuscular injection is 25 to 50 mg repeated every 6 to 8 hours if required, although oral therapy should be substituted as soon as possible.

If the oral and parenteral routes are not suitable chlorpromazine may be given *rectally* as suppositories containing 100 mg of chlorpromazine base; this is stated to have an effect comparable with 40 to 50 mg of the hydrochloride orally or 20 to 25 mg intramuscularly. The usual rectal dose is 100 mg every 6 to 8 hours.

Initial oral doses of chlorpromazine of one-third to one-half the usual adult dose have been recommended for *elderly* or *debilitated patients*; doses should be increased more gradually. Intramuscular doses in the elderly may need to be reduced to up to one-quarter of the usual dose.

Doses of 10 to 25 mg every 4 to 6 hours orally are recommended for control of **nausea and vomiting**. If necessary, an initial dose of 25 mg may be given by intramuscular injection, followed by 25 to 50 mg every 3 to 4 hours until vomiting stops.

If **intractable hiccup** does not respond to an oral dose of 25 to 50 mg three or four times daily for 2 to 3 days then 25 to 50 mg may be given intramuscularly; if this fails 25 to 50 mg in 500 to 1000 mL of 0.9% sodium chloride should be given by slow intravenous infusion, with the patient supine, and careful monitoring of the blood pressure.

For details of doses in *children*, see below.

Action. The therapeutic effects of antipsychotics appear to be mediated, at least in part, by interference with dopamine transmission in the brain. Chlorpromazine, thioridazine, and thioxanthene derivatives have relatively equal affinity for D_1 or D_2 receptors, although their metabolites tend to be more potent as D_2 blockers.[1] Butyrophenones (such as haloperidol) and diphenylbutylpiperidines (such as pimozide) are relatively selective for D_2 receptors, and the substituted benzamides (such as sulpiride) are highly D_2-specific. Clozapine has complex actions: it is a relatively weak inhibitor of D_2 receptors but has a high affinity for several other receptors including D_1, D_4, and serotonin$_2$ ($5\text{-}HT_2$) receptors.[2] Other atypicals mostly share this profile of greater $5\text{-}HT_2$ than D_2 antagonism.[2]

The traditional hypothesis of the action of antipsychotics has been that blockade of D_2 receptors in the limbic and cortical regions is responsible for the antipsychotic effects, and that adverse extrapyramidal motor effects result from blockade of D_2 receptors in the striatum (a typical motor region of the basal ganglia).[3] Modification of prolactin secretion results from blockade of D_2 receptors in the anterior pituitary. However, this hypothesis cannot satisfactorily account for the pharmacological profiles of atypical antipsychotics and the debate concerning their mechanism of action continues. It has been suggested that the balance between $5\text{-}HT_2$ and D_2 antagonism is important in determining 'atypicality' (but the atypical antipsychotic amisulpride lacks marked $5\text{-}HT_2$ antagonism), or that rapid dissociation from the D_2 receptor may be the determining factor (but it is not clear that some atypicals such as risperidone meet this criterion).[2] Other systems, such as glutamate, may play a role in modulating efficacy against negative versus positive symptoms;[2] it has been suggested that the calcium antagonist actions of the diphenylbutylpiperidines may also be important in this respect.[4]

Division of antipsychotics into low- and high-potency drugs is discussed in Administration, below. For reference to the actions of antipsychotics on neuroendocrine function, see Effects on Endocrine Function under Adverse Effects, p. 1048.2.

1. Ereshefsky L, *et al.* Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9**: 682–707.
2. Remington G. Understanding antipsychotic 'atypicality': a clinical and pharmacological moving target. *J Psychiatry Neurosci* 2003; **28**: 275–84.
3. Anonymous. Now we understand antipsychotics? *Lancet* 1990; **336**: 1222–3.
4. Snyder SH. Drug and neurotransmitter receptors: new perspectives with clinical relevance. *JAMA* 1989; **261**: 3126–9.

Administration. The classical antipsychotics are often divided into:

- **low-potency** drugs (phenothiazines with an aliphatic or piperidine side-chain or thioxanthenes with an aliphatic side-chain)
- **high-potency** drugs (butyrophenones, diphenylbutylpiperidines, and phenothiazines or thioxanthenes with a piperazine side-chain)

At doses with equipotent antipsychotic activity, the low-potency drugs are more prone to cause sedation and antimuscarinic or α-adrenergic-blocking effects than the high-potency drugs. However, they are associated with a lower incidence of extrapyramidal effects, with the exception of tardive dyskinesia which is likely to occur to the same extent with all classical antipsychotics.

Equivalent doses of antipsychotics quoted in the literature have varied considerably. In the UK the following daily doses of oral antipsychotics have been suggested to have approximately equipotent antipsychotic activity for doses up to the maximum licensed doses:

- chlorpromazine hydrochloride 100 mg
- clozapine 50 mg
- haloperidol 2 to 3 mg
- pimozide 2 mg
- risperidone 0.5 to 1 mg
- sulpiride 200 mg
- thioridazine 100 mg
- trifluoperazine 5 mg

It should be noted that all patients receiving pimozide require an ECG before, and periodically during, treatment (see p. 1097.2). Droperidol and thioridazine also require specialist supervision (see p. 1072.1 and p. 1110.3, respectively).

Suggested equipotent doses of intramuscular depot antipsychotics are:

- flupentixol decanoate 40 mg every 2 weeks
- fluphenazine decanoate 25 mg every 2 weeks
- haloperidol (as the decanoate) 100 mg every 4 weeks
- pipotiazine palmitate 50 mg every 4 weeks
- zuclopenthixol decanoate 200 mg every 2 weeks

It has been noted[1] that *high doses* of antipsychotics (greater than the equivalent of 600 mg of chlorpromazine daily) are generally not necessary for the treatment (both initial and maintenance) of psychotic disorders, and may be associated with an increased risk of adverse effects as well as with a diminished clinical response. However, if high doses of antipsychotics have to be used, then doses should be increased gradually with caution and under the supervision of a specialist with facilities for emergency resuscitation available. The Royal College of Psychiatrists in the UK (which defines high-dose therapy as that involving a total daily dose greater than the upper limit recommended in the *BNF*) has issued recommendations concerning the use of high-dose antipsychotic medication.[2] It considers:

- current evidence does not justify the routine use of high-dose therapy with antipsychotics
- if high-dose therapy is used, this should only be after evidence-based strategies have failed, and as a carefully-monitored therapeutic trial
- the decision to use high-dose therapy, and the expected outcome, should be fully documented, after expert assessment of the patient
- the possible contra-indications to therapy, and the risk of drug interactions, should be assessed beforehand
- an ECG should be carried out before starting high-dose therapy and should be repeated after a few days, and then every 1 to 3 months in the early stages of treatment, or as clinically indicated
- doses should be increased in relatively small increments, with time to assess response before a further increase
- the use of 'as-required' antipsychotic medication, and of drug combinations, should be carefully monitored to avoid the inadvertent increase of total doses above high-dose thresholds

The existence of a *therapeutic range* (or therapeutic window) has not been found for most antipsychotics (with the possible exception of haloperidol[3]), and plasma concentrations of these drugs must be interpreted with caution.[1,3] Many factors make it difficult to establish a meaningful correlation between dose, plasma concentrations, and clinical improvement. These include incomplete absorption, first-pass effect, enzyme induction, the presence of active and inactive metabolites, ethnicity, smoking, and factors occurring at the receptor level.[3]

1. Baldessarini RJ, *et al.* Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988; **45**: 77–91.
2. The Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. *Council Report CR138*; London: Royal College of Psychiatrists, May 2006. Available at: http://www.rcpsych.ac.uk/files/pdfversion/CR138.pdf (accessed 30/05/06)
3. Sramek JJ, *et al.* Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22**: 373–80.

Administration in children. Chlorpromazine is used in children for the management of acute and chronic schizophrenia, control of severely disturbed, agitated, or violent behaviour, autism, to reduce pre-operative anxiety, and as an antiemetic in some forms of nausea and vomiting. It has also been used for induction of hypothermia.

Chlorpromazine hydrochloride may be given to children aged 1 to 12 years in a dose of 500 micrograms/kg every 4 to 6 hours orally or every 6 to 8 hours by intramuscular injection. However, for psychiatric indications the oral dose for children aged 6 to 12 years is usually one-third to one-half the usual adult dose (see p. 1045.3); alternatively, the *BNFC* suggests an oral dose of 10 mg 3 times daily. To reduce pre-operative anxiety a single oral dose is given 2 to 3 hours before the procedure. For all indications, daily doses should not normally exceed 40 mg of chlorpromazine hydrochloride in children aged 1 to 5 years or 75 mg in those aged 6 to 12 years. Chlorpromazine may be given to infants under 1 year of age if considered to be life-saving. Children and adolescents aged 12 years and over may be given usual adult doses, see p. 1045.3.

For reference to the use of lytic cocktails containing chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see Lytic Cocktails, under Sedation, p. 122.2.

Bipolar disorder. Patients with bipolar disorder (p. 397.2) suffering from acute mania with coexisting psychotic features, agitation, or disruptive behaviour are usually treated with antipsychotics as they produce rapid control of symptoms. Classical antipsychotics such as chlorpromazine or haloperidol have been widely used, although use of atypical antipsychotics, such as clozapine or olanzapine, is growing.

Chorea. For a discussion of the management of various choreas, including mention of the use of phenothiazines such as chlorpromazine, see p. 1029.3.

Dyspnoea. It has been shown that in healthy subjects an oral dose of 25 mg of chlorpromazine hydrochloride can reduce exercise-induced breathlessness without affecting ventilation or causing sedation.[1] Although other drugs may be preferred in patients with advanced cancer and dyspnoea (p. 108.3), chlorpromazine may relieve air hunger unresponsive to usual measures,[2] and, if required, can be used to sedate dying patients who have unrelieved distress. It is recommended that initial doses should be small: 12.5 mg by slow intravenous injection or 25 mg by suppository may be given.

1. O'Neill PA, *et al.* Chlorpromazine—a specific effect on breathlessness? *Br J Clin Pharmacol* 1985; **19**: 793–7.
2. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342**: 450–1.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to other drugs.[1] However, they often act non-specifically, damping down excessive movements by causing a degree of drug-induced parkinsonism and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders, under Adverse Effects, p. 1049.2).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300**: 139–44.

Eclampsia and pre-eclampsia. Drug combinations known as lytic cocktails have been used in many countries for the management of pre-eclampsia and imminent eclampsia. The cocktail has usually consisted of a combination of chlorpromazine, pethidine, and/or promethazine. In general, however, phenothiazines are not recommended in late pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p. 1251.1); the management of eclampsia, which is the convulsive phase, is discussed on p. 511.1.

Headache. Some phenothiazines such as chlorpromazine, levomepromazine, and prochlorperazine have been used in migraine to control severe nausea and vomiting unresponsive to antiemetics such as metoclopramide and domperidone (see p. 670.3), and to relieve the pain of severe migraine attacks unresponsive to parenteral dihydroergotamine or sumatriptan.

References.

1. Stiell IG, *et al.* Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20**: 1201–5.
2. Jones EB, *et al.* Safety and efficacy of rectal prochlorperazine for the treatment of migraine in the emergency department. *Ann Emerg Med* 1994; **24**: 237–41.
3. Coppola M, *et al.* Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26**: 541–6.
4. Jones J, *et al.* Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14**: 262–4.
5. Kelly AM, *et al.* Intravenous chlorpromazine versus intramuscular sumatriptan for acute migraine. *J Accid Emerg Med* 1997; **14**: 209–11.
6. Bigal ME, *et al.* Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med* 2002; **23**: 141–8.

Hiccup. A hiccup is an involuntary spasmodic contraction of the diaphragm that causes a sudden inspiration of air which is then checked abruptly by closure of the glottis. Hiccups often have a simple cause such as gastric distension and usually resolve spontaneously or respond to simple measures. Intractable hiccups may stem from a serious underlying cause such as brain disorders, metabolic or endocrine disturbances, CNS infections, and oesophageal or other gastrointestinal disorders. Other precipitants include anaesthesia or drug therapy.

Treatment of intractable hiccups should initially be aimed at controlling or removing the underlying cause including the relief of gastric distension or oesophageal obstruction.[1-5] Measures that raise carbon dioxide pressure such as breath holding, rebreathing, or alteration of normal respiratory rhythm can be effective. Stimulation of the pharynx can also interrupt hiccups and may explain the action of a host of remedies such as sipping iced water, gargling, and swallowing granulated sugar. Many drugs have been tried in the treatment of hiccups but evidence of efficacy is largely from anecdotal reports or uncontrolled studies. An early treatment protocol[6] for intractable hiccup (based on a review of the literature and the authors experience) suggested stepwise management until an effective measure was found, as follows:

- correction of any metabolic abnormality
- swallowing dry granulated sugar
- decompressing the stomach via nasogastric tube, then irritation of the pharynx
- intravenous chlorpromazine 25 to 50 mg, repeated up to 3 times if necessary; if parenteral therapy is effective maintain on oral chlorpromazine for 10 days (licensed

information recommends the use of oral therapy first — see Uses and Administration, p. 1045.3)
- metoclopramide 10 mg intravenously; if successful maintain on oral metoclopramide for 10 days
- oral quinidine 200 mg 4 times daily
- if this fails, consider left phrenic nerve block and crush

In later discussions,[1,3] chlorpromazine still emerged as the most consistently effective drug treatment; metoclopramide appeared to be an acceptable second choice and nifedipine an appropriate third choice,[3] although haloperidol was also considered to be of value.[1,4] Other phenothiazines that have been used for intractable hiccup include perphenazine and promazine. It was also considered that clonazepam, carbamazepine, phenytoin, and valproic acid might be of value, especially in neuropathic hiccups.[1] Some beneficial results have been reported with amitriptyline and amantadine; other drugs being tried in the treatment of hiccups include baclofen and gabapentin. The *BNF* recommends that in palliative care patients, a preparation combining an antacid with an antiflatulent be given for hiccups due to gastric distension. If this fails, metoclopramide (orally or by subcutaneous or intramuscular injection) should be added; baclofen, nifedipine, or chlorpromazine should be reserved for those patients in whom metoclopramide is also ineffective.

1. Howard RS. Persistent hiccups: if excluding or treating any underlying pathology fails try chlorpromazine. *BMJ* 1992; 305: 1237–8.
2. Rousseau P. Hiccups. *South Med J* 1995; 88: 175–81.
3. Friedman NL. Hiccups: a treatment review. *Pharmacotherapy* 1996; 16: 986–95.
4. WHO. Hiccup. In: *Symptom relief in terminal illness*. Geneva: WHO, 1998.
5. Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. *Am J Hosp Palliat Care* 2003; 20: 149–54.
6. Williamson BWA, Macintyre IMC. Management of intractable hiccup. *BMJ* 1977; 2: 501–3.

Lesch-Nyhan syndrome. The Lesch-Nyhan syndrome is an inherited disorder caused by a complete deficiency of hypoxanthine-guanine phosphoribosyl transferase, an enzyme involved in purine metabolism. It is characterised by hyperuricaemia, spasticity, choreoathetosis, self-mutilation, and mental retardation. The hyperuricaemia (see p. 600.1) can be controlled by drugs such as allopurinol but there appears to be no effective treatment for the neurological deficits. It has been suggested that the behavioural problems might be associated with alterations in the brain's dopamine system. There have been rare reports of improvement in self-mutilation in patients given antipsychotics or antiepileptics such as carbamazepine and gabapentin.

References.
1. Nyhan WL, Wong DF. New approaches to understanding Lesch-Nyhan disease. *N Engl J Med* 1996; 334: 1602–4.

Migraine. See under Headache, p. 1046.3.

Nausea and vomiting. Many antipsychotics, with the notable exception of thioridazine, have antiemetic properties and have been used in the prevention and treatment of nausea and vomiting (p. 1814.3) arising from a variety of causes such as radiation sickness, malignancy, and emesis caused by drugs, including antineoplastics and opioid analgesics. Reference to the risk to the fetus of therapy with phenothiazines during pregnancy can be found under Precautions, p. 1051.3 and on p. 614.2.

Schizophrenia. Classical antipsychotics such as chlorpromazine, haloperidol, and thioridazine have been the traditional drug treatment of choice for patients with schizophrenia (p. 1031.3); however, atypical antipsychotics may now be preferred as first-line therapy. There is little difference in efficacy between the classical antipsychotics, but the use of thioridazine is now restricted in the treatment of schizophrenia because of the risk of cardiotoxicity.

Substance dependence. *ALCOHOL* For advice against the use of antipsychotics for alcohol withdrawal, see p. 1735.1.

OPIOIDS. In a discussion of neonatal abstinence syndrome (p. 110.1), it was noted in 1986 that, although opioids, diazepam, and phenobarbital were widely used in the USA for the management of this condition, chlorpromazine had tended to be the preferred treatment in the UK.[1] This was still true as late as the mid-1990s, although practice varied widely.[2] However, a systematic review[3] found insufficient evidence to support the use of chlorpromazine in the management of neonatal abstinence syndrome. The following dosage schedule has been suggested:[1] chlorpromazine is begun with a loading dose of 3 mg/kg, followed by a total oral maintenance dose of 3 mg/kg daily, divided into 4 or 6 doses. The authors suggested that this dose might be increased by 3 mg/kg daily if withdrawal symptoms were particularly severe. Once stabilised a reduction in the dose of chlorpromazine by 2 mg/kg every third day is attempted.[1] Complications of phenothiazine usage have been notably absent, although rarely seizures may occur.

1. Rivers RPA. Neonatal opiate withdrawal. *Arch Dis Child* 1986; 61: 1236–9.
2. Morrison CL, Siney C. A survey of the management of neonatal opiate withdrawal in England and Wales. *Eur J Pediatr* 1996; 155: 323–6.
3. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 02/10/07).

Taste disorders. Disturbances of the sense of taste may be broadly divided into either loss or distortion of taste. Loss of taste may be either complete (ageusia) or partial (hypogeusia). Distortion of taste (dysgeusia) may occur as aliageusia in which stimuli such as food or drink produce an inappropriate taste or as phantogeusia in which an unpleasant taste is not associated with an external stimuli and is sometimes referred to as a gustatory hallucination. Taste disturbances have many causes including infections, metabolic or nutritional disturbances, radiation, CNS disorders, neoplasms, drug therapy, or may occur as a consequence of normal ageing.[1] Management mainly consists of treatment of any underlying disorder. Withdrawal of offending drug therapy is commonly associated with resolution but occasionally effects persist and may require treatment.[2] Zinc or vitamin therapy has been used but there is insufficient evidence to indicate efficacy[1,3] for taste disturbances secondary to drug therapy or medical conditions that do not involve low zinc or vitamin concentrations. Phantogeusia might be linked to excessive activity of dopaminergic receptors as it has been reported[4] to respond to short-term treatment with small doses of antipsychotic drugs such as haloperidol or pimozide.

1. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA* 1997; 278: 1357–62.
2. Henkin RI. Drug-induced taste and smell disorders: incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Safety* 1994; 11: 318–77.
3. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; 30: 186–7.
4. Henkin RI. Salty and bitter taste. *JAMA* 1991; 265: 2253.

Adverse Effects

Chlorpromazine generally produces less central depression than the barbiturates or benzodiazepines, and tolerance to its initial sedative effects develops fairly quickly in most patients. It has antimuscarinic properties and may cause adverse effects such as dry mouth, constipation, difficulty with micturition, blurred vision, and mydriasis. Tachycardia, ECG changes (particularly Q-and T-wave abnormalities), and, rarely, cardiac arrhythmias may occur; hypotension (usually orthostatic) is common. Other adverse effects include delirium, agitation and, rarely, catatonic-like states, insomnia or drowsiness, nightmares, depression, miosis, EEG changes and convulsions, nasal congestion, precipitation of glaucoma, minor abnormalities in liver function tests, inhibition of ejaculation, impotence, and priapism.

Hypersensitivity reactions include urticaria, exfoliative dermatitis, erythema multiforme, and contact sensitivity. A syndrome resembling SLE has been reported. Jaundice has occurred, and probably has an immunological origin. Prolonged therapy may lead to deposition of pigment in the skin, or more frequently the eyes; corneal and lens opacities have occurred. Pigmentary retinopathy has occurred only rarely with chlorpromazine. Photosensitivity reactions are more common with chlorpromazine than with other antipsychotics.

Haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, and a potentially fatal agranulocytosis have occasionally been reported; they may be manifestations of a hypersensitivity reaction. Most cases of agranulocytosis have occurred within 4 to 10 weeks of starting treatment, and symptoms such as sore throat or fever should be watched for and white cell counts instituted should they appear. Mild leucopenia has been stated to occur in up to 30% of patients on prolonged high dosage.

Extrapyramidal dysfunction and resultant disorders include acute dystonia, a parkinsonism-like syndrome, and akathisia; late effects include tardive dyskinesia and perioral tremor. The neuroleptic malignant syndrome may also occur.

Chlorpromazine alters endocrine and metabolic functions. Patients have developed amenorrhoea, galactorrhoea, and gynaecomastia due to hyperprolactinaemia, weight gain, and hyperglycaemia and altered glucose tolerance. Body temperature regulation is impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

There have been isolated reports of sudden death with chlorpromazine; possible causes include cardiac arrhythmias or aspiration and asphyxia due to suppression of the cough and gag reflexes.

Pain and irritation at the injection site may occur on injection. Nodule formation may occur after intramuscular injection.

Phenothiazines do not cause dependence of the type encountered with barbiturates or benzodiazepines. However, withdrawal symptoms have been seen on abrupt withdrawal in patients receiving prolonged and/or high-dose maintenance therapy.

Although the adverse effects of **other phenothiazines** are broadly similar in nature to those of chlorpromazine, their frequency and pattern tend to fall into 3 groups:
- group 1 (e.g. chlorpromazine, levomepromazine, and promazine) are generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal effects
- group 2 (e.g. pericyazine, pipotiazine, and thioridazine) are generally characterised by moderate sedative effects, marked antimuscarinic effects, and fewer extrapyramidal effects than groups 1 or 3
- group 3 (e.g. fluphenazine, perphenazine, prochlorperazine, and trifluoperazine) are generally characterised by fewer sedative and antimuscarinic effects but more pronounced extrapyramidal effects than groups 1 or 2

Classical antipsychotics of **other chemical groups** tend to resemble the phenothiazines of group 3. They include the butyrophenones (e.g. benperidol and haloperidol); diphenylbutylpiperidines (e.g. pimozide); thioxanthenes (flupentixol and zuclopenthixol); substituted benzamides (e.g. sulpiride); oxypertine; and loxapine.

Carcinogenicity. See Effects on Endocrine Function, p. 1048.2.

Convulsions. Treatment with antipsychotics can result in EEG abnormalities and lowered seizure threshold.[1] Seizures can be induced particularly in patients with a history of epilepsy or drug-induced seizures, abnormal EEG, previous electroconvulsive therapy, or pre-existing CNS abnormalities. The risk appears to be greatest at the start of antipsychotic therapy, or with high doses, or abrupt increases of dose, or with the use of more than one antipsychotic. The incidence of antipsychotic-induced convulsions is, however, probably less than 1%.

In general, the epileptic potential has been correlated with the propensity of the antipsychotic to cause sedation. Phenothiazines with marked sedative effects [group 1] such as chlorpromazine appear to present a higher risk than those with strong extrapyramidal effects [group 3]. Haloperidol appears to carry a relatively low risk of seizures. The following drugs have been suggested when classical antipsychotic therapy is considered necessary in patients at risk of seizures or being treated for epilepsy: fluphenazine, haloperidol, pimozide, or trifluoperazine. Antipsychotic dosage should be increased slowly and the possibility of interactions with antiepileptic therapy considered (see under Interactions, p. 1052.2).

The atypical antipsychotic clozapine appears to be associated with a particularly high risk of seizures (see Effects on the Nervous System, under Clozapine, p. 1060.1). Risperidone may be preferred if an atypical antipsychotic is to be used in patients at risk of seizures.

1. Pisani P, *et al.* Effects of psychotropic drugs on seizure threshold. *Drug Safety* 2002; 25: 91–110.

Effects on the blood. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them phenothiazines for which there were 87 reports of agranulocytosis (42 fatal) and 33 of neutropenia (22 fatal). The most frequently implicated phenothiazines were chlorpromazine with 51 reports of agranulocytosis (26 fatal) and 12 of neutropenia (2 fatal) and thioridazine with 20 reports of agranulocytosis (9 fatal) and 10 of neutropenia (none fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; 19: 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2044566&RevisionSelectionMethod=LatestReleased (accessed 18/07/08)

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. For further details, see Effects on Body-weight, in Clozapine, p. 1059.1.

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; 156: 1686–96.

Effects on the cardiovascular system. Orthostatic hypotension is a common problem in patients taking psychotropic drugs and is particularly pronounced with low-potency antipsychotics.[1]

Various **ECG changes** or frank **arrhythmias** have occurred in patients receiving antipsychotics. T-wave changes have been reported with low-potency antipsychotics; they are usually benign and reversible, and subject to diurnal fluctuations. Low-potency antipsychotics, particularly *thioridazine* and *mesoridazine*, and the high-potency drug *pimozide*, prolong the QT interval in a similar manner to class I antiarrhythmics such as quinidine or procainamide; their use is therefore contra-indicated in patients taking such antiarrhythmics. *Droperidol*, another high-potency drug, has also been reported to prolong the QT interval.[2] Thioridazine is most frequently discussed in case reports of psychotropic drug-induced torsade de pointes;[2] *chlorpromazine* and *pimozide* have also been implicated. The increased risk of QT prolongation with droperidol, mesoridazine, and thioridazine have led to restrictions on their use; for further details see individual monographs. Torsade de pointes has also been reported after overdosage[3-5] with, or high intravenous[6] doses of, the high-potency antipsychotic *haloperidol*. There are also isolated reports of cardiac arrhythmias after attempts at rapid control with high doses of haloperidol.[7,8] *Melperone*, a butyrophenone antipsychotic related to haloperidol, has been reported to have class III electrophysiologic and antiarrhythmic activity.[9,10]

In the UK, the risk of arrhythmias with antipsychotic treatment has been considered by an expert working group of the CSM;[11] the following recommendations were made regarding ECG monitoring:

- the need for an ECG should be based on a patient's relevant medical history, family history, and clinical examination; the elderly and those with a personal or family history of heart disease or any cardiac abnormalities would benefit the most from a baseline ECG (Licensed product information for both pimozide and thioridazine recommend that an ECG should be performed in all patients before starting treatment with either of these drugs.)
- during treatment an ECG should be performed in patients who have palpitations or other symptoms suggestive of cardiac disease; if the QT interval is prolonged then a reduction in dose may be required, if it exceeds 500 milliseconds treatment may need to be stopped
- an ECG should be considered during dose increases
- potassium levels should be monitored before and during treatment and in particular during periods of acute illnesses

Sudden unexpected deaths have been reported in patients receiving classical or atypical antipsychotics.[12] Whether this is due to the disease being treated or to the treatment is still unclear. However, in a retrospective cohort study[13] involving about 482 000 patients, analysis of 1487 sudden cardiac deaths indicated that patients receiving classical antipsychotics in doses of more than 100 mg of thioridazine or its equivalent had a 2.4-fold increase in the rate of sudden cardiac death, rising to a 3.53-fold increase in those patients with pre-existing severe cardiovascular disease. A later case-control study[14] in 5 UK psychiatric hospitals found that sudden unexplained death in psychiatric patients was associated with hypertension, ischaemic heart disease, and current treatment with thioridazine. Although several mechanisms have been suggested for the effect, prolongation of the QT interval has been implicated in a proportion of the cases.[12] More recently, in a retrospective cohort study,[15] involving 93 300 antipsychotic users (44 218 used classical antipsychotics and 46 089 used atypicals) and 186 600 matched controls of non-users, analyses of 1870 sudden cardiac deaths that occurred during the approximately 1 million patient-years of follow-up concluded that current users of classical or atypical antipsychotics had a similar dose-related increased risk of sudden cardiac death when compared with non-users; former users had no significantly increased risk. The excess mortality may also in part be due to the poor health outcomes of some patients with schizophrenia because of lack of appropriate health care. An 11-year follow-up cohort study[16] in schizophrenics concluded that all-cause mortality was decreased with the long-term use of classical or atypical antipsychotics when compared with no antipsychotic use. In addition, the study also found that current use of clozapine was associated with the lowest mortality rate when compared with current use of perphenazine; quetiapine, haloperidol, and risperidone had the highest rates.

Results from a case-control study[17] have suggested that use of classical antipsychotics may be associated with an increased risk of idiopathic **venous thromboembolism.** The risk was most pronounced during the first 3 months of treatment, and was higher for low-potency than high-potency antipsychotics; this study did not examine the risk of venous thromboembolism with atypical antipsychotics. A more recent analysis[18] of the WHO database of adverse drug reactions found no association between venous thromboembolism and the use of low-potency or high-potency classical antipsychotics when considered as 2 groups; however, a statistically significant association was found with the use of zuclopenthixol, a high-potency drug, when considered on its own. A robust association was also found with the use of atypical antipsychotics—see also under Clozapine, p. 1059.3. Nevertheless, the authors acknowledged the limitations of this study such as reporting bias and incomplete clinical data, and further investigation was considered warranted.

1. DiGiacomo J. Cardiovascular effects of psychotropic drugs. *Cardiovasc Rev Rep* 1989; **10**: 31–2, 39–41, and 47.
2. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355**: 1048–52.
3. Zee-Cheng C-S, *et al.* Haloperidol and torsades de pointes. *Ann Intern Med* 1985; **102**: 418.
4. Henderson RA, *et al.* Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. *Hum Exp Toxicol* 1991; **10**: 59–62.
5. Wilt JL, *et al.* Torsade de pointes associated with the use of intravenous haloperidol. *Ann Intern Med* 1993; **119**: 391–4.
6. O'Brien JM, *et al.* Haloperidol-induced torsade de pointes. *Ann Pharmacother* 1999; **33**: 1046–50.
7. Mehta D, *et al.* Cardiac arrhythmia and haloperidol. *Am J Psychiatry* 1979; **136**: 1468–9.
8. Bett JHN, Holt GW. Malignant ventricular tachyarrhythmia and haloperidol. *BMJ* 1983; **287**: 1264.
9. Magelvang JC, *et al.* Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; **208**: 61–4.
10. Hui WKK, *et al.* Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; **15**: 144–9.
11. CSM/MHRA. Cardiac arrhythmias associated with antipsychotic drugs. *Current Problems* 2006; **31**: 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
12. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 2002; **62**: 1649–71.
13. Ray WA, *et al.* Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; **58**: 1161–7.
14. Reilly JG, *et al.* Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry* 2002; **180**: 515–22.
15. Ray WA, *et al.* Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; **360**: 225–35. Correction. *ibid.*; **361**: 1814.
16. Tiihonen J, *et al.* 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; **374**: 620–7.
17. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000; **356**: 1219–23.
18. Hägg S, *et al.* Associations between venous thromboembolism and antipsychotics: a study of the WHO database of adverse drug reactions. *Drug Safety* 2008; **31**: 685–94.

Effects on endocrine function. Antipsychotics can alter the secretion of prolactin, growth hormone, and thyrotrophin from the anterior pituitary via their ability to block central dopamine-D_2 receptors. Therapeutic doses of classical antipsychotics (and some atypical antipsychotics such as amisulpride and risperidone) increase serum-prolactin concentrations; this effect occurs at lower doses and after shorter latent periods than the antipsychotic effects. However, partial tolerance to the hyperprolactinaemic effect may develop on long-term use.[1] Serum prolactin declines to normal values within 3 weeks of stopping oral antipsychotic therapy but may remain raised for 6 months after an intramuscular depot injection.[1]

The long-term consequences of gonadal hormone deficiency, secondary to raised prolactin concentrations, have caused concern. There is evidence[2] that patients taking long-term prolactin-raising antipsychotics are at high risk of osteoporosis associated with hypogonadism. Long-term antipsychotic treatment has also been shown to increase the incidence of mammary tumours in the *rat*. Although early studies[3,4] found little or no evidence that chronic use in humans alters the risk of breast cancer among women with schizophrenia, a later retrospective cohort study[5] found a modest dose-related increase in the risk of breast cancer in women using antipsychotic dopamine antagonists. A similar increase was seen in women receiving antiemetic dopamine antagonists. Fears that pituitary abnormalities, including pituitary tumours,[6] might develop in patients on long-term phenothiazine therapy have not been confirmed.[7,8]

Antipsychotics can in some circumstances reduce both basal and stimulated growth-hormone secretion but attempts to use them to treat dysfunctions in growth-hormone regulation have not been successful.[9] Although some clinical studies show that acute dosage of antipsychotics increased both basal and stimulated thyrotrophin secretion, the majority of studies find either no change or only a small increase in thyrotrophin secretion following long-term use.

A small study[10] has suggested that thioridazine may be more likely than other antipsychotics to decrease serum concentrations of testosterone or luteinising hormone in men. However, concentrations were within the normal range in most patients taking antipsychotics.

See also Effects on Fluid and Electrolyte Homoeostasis, below and Effects on Sexual Function, p. 1049.1.

1. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; **64**: 2291–2314.
2. Meaney AM, *et al.* Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *Br J Psychiatry* 2004; **184**: 503–8.
3. Mortensen PB. The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health* 1989; **43**: 43–7.
4. Mortensen PB. The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res* 1994; **12**: 185–94.
5. Wang PS, *et al.* Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry* 2002; **59**: 1147–54.
6. Asplund K, *et al.* Phenothiazine drugs and pituitary tumors. *Ann Intern Med* 1982; **96**: 533.
7. Rosenblatt S, *et al.* Chronic phenothiazine therapy does not increase sellar size. *Lancet* 1978; **ii**: 319–20.
8. Lilford VA, *et al.* Long-term phenothiazine treatment does not cause pituitary tumours. *Br J Psychiatry* 1984; **144**: 421–4.
9. Gunnet JW, Moore KE. Neuroleptics and neuroendocrine function. *Ann Rev Pharmacol Toxicol* 1988; **28**: 347–66.
10. Brown WA, *et al.* Differential effects of neuroleptic agents on the pituitary-gonadal axis in men. *Arch Gen Psychiatry* 1981; **38**: 1270–2.

Effects on the eyes. Phenothiazines may induce a pigmentary retinopathy that is dependent on both the dose and the duration of treatment.[1] Those phenothiazine derivatives with piperidine side-chains such as thioridazine have a higher risk of inducing retinal toxicity than other phenothiazine derivatives, with relatively few cases reported for those with aliphatic side-chains such as chlorpromazine; the piperazine group does not appear to exert direct ocular toxicity.[2] The retinopathy may present either acutely, (sudden loss of vision associated with retinal oedema and hyperaemia of the optic disc), or chronically (a fine pigment scatter appearing in the central area of the fundus, extending peripherally but sparing the macula). Chronic paracentral and pericentral scotomas may be found. Although pigmentary disturbances may progress after withdrawal of thioridazine, they are not always paralleled by deterioration in visual function; nonetheless, some cases have led to progressive chorioretinopathy.[3] The critical ocular toxic dose of thioridazine is reported to be 800 mg daily[1] and UK licensed product information has recommended that a daily dose of 600 mg should not usually be exceeded. However, there is a report[4] of pigmentary retinopathy in a patient who received long-term thioridazine in daily doses not exceeding 400 mg; the total dose was 752 g.

Pigmentation may also occur in the cornea, lens, and conjunctiva following use of phenothiazines. It may occur in association with pigmentary changes in the skin and is dose-related. In a study of 100 Malaysian patients, ocular pigmentation occurred in slightly more than half of those who had received a total dose of chlorpromazine of 100 to 299 g and in 13 of 15 who had received 300 to 599 g.[5] All those who had received more than 600 g of chlorpromazine or thioridazine had ocular pigmentation. Cataract formation, mainly of an anterior polar variety, has been seen rarely, mainly in patients on chlorpromazine. It does not appear to be dose-related.[2]

A patient who had received fortnightly injections of fluphenazine 12.5 mg for 10 years (total dose 3.25 g) developed bilateral maculopathy after unprotected exposure of less than 2-minute's duration to a welding arc.[6] It was postulated that accumulation of phenothiazine in the retinal epithelium sensitised the patient to photic damage. However, another patient who had received fortnightly injections of fluphenazine 25 mg for 2½ years (total dose 16.25 g) developed bilateral maculopathy without exposure to any extreme photochemical sources.[7] The authors concluded that this was due to a direct effect of fluphenazine secondary to its accumulation in the retinal epithelium.

1. Spiteri MA, James DG. Adverse ocular reactions to drugs. *Postgrad Med J* 1983; **59**: 343–9.
2. Crombie AL. Drugs causing eye problems. *Prescribers' J* 1981; **21**: 222–7.
3. Marmor MF. Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function. *Br J Ophthalmol* 1990; **74**: 739–42.
4. Lam RW, Remick RA. Pigmentary retinopathy associated with low-dose thioridazine treatment. *Can Med Assoc J* 1985; **132**: 737.
5. Ngen CC, Singh P. Long-term phenothiazine administration and the eye in 100 Malaysians. *Br J Psychiatry* 1988; **152**: 278–81.
6. Power WJ, *et al.* Welding arc maculopathy and fluphenazine. *Br J Ophthalmol* 1991; **75**: 433–5.
7. Lee MS, Fern AI. Fluphenazine and its toxic maculopathy. *Ophthalmic Res* 2004; **36**: 237–9.

Effects on fluid and electrolyte homoeostasis. There have been occasional reports of water intoxication in patients taking antipsychotics. A review[1] of hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion associated with psychotropics summarised 20 such reports for antipsychotics in the literature. The drugs implicated were thioridazine (8 reports), haloperidol (3 reports), chlorpromazine, trifluoperazine, and fluphenazine (2 reports each), and flupentixol, tiotixene, and clozapine (1 report each). The majority of reports did not permit clear conclusions and, particularly in the cases of prolonged treatment, the role of the medication was unclear. However, at least 3 of the cases were well documented and supported the view that antipsychotics could cause hyponatraemia. A more recent review[2] has also concluded that both classical and atypical antipsychotics may induce hyponatraemia.

A report not considered by the above review described water retention and peripheral oedema associated with chlorpromazine.[3] A small controlled study[4] found that 5 of

1. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; **64**: 2291–2314.
2. Meaney AM, *et al.* Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *Br J Psychiatry* 2004; **184**: 503–8.
3. Mortensen PB. The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health* 1989; **43**: 43–7.
4. Mortensen PB. The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res* 1994; **12**: 185–94.
5. Wang PS, *et al.* Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry* 2002; **59**: 1147–54.
6. Asplund K, *et al.* Phenothiazine drugs and pituitary tumors. *Ann Intern Med* 1982; **96**: 533.
7. Rosenblatt S, *et al.* Chronic phenothiazine therapy does not increase sellar size. *Lancet* 1978; **ii**: 319–20.
8. Lilford VA, *et al.* Long-term phenothiazine treatment does not cause pituitary tumours. *Br J Psychiatry* 1984; **144**: 421–4.
9. Gunnet JW, Moore KE. Neuroleptics and neuroendocrine function. *Ann Rev Pharmacol Toxicol* 1988; **28**: 347–66.
10. Brown WA, *et al.* Differential effects of neuroleptic agents on the pituitary-gonadal axis in men. *Arch Gen Psychiatry* 1981; **38**: 1270–2.

10 evaluated patients receiving haloperidol decanoate had impaired fluid homoeostasis.

1. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; 12: 209–25.
2. Meulendijks D, *et al.* Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. *Drug Safety* 2010; 33: 101–14.
3. Witz L, *et al.* Chlorpromazine induced fluid retention masquerading as idiopathic oedema. *BMJ* 1987; 294: 807–8.
4. Rider JM, *et al.* Water handling in patients receiving haloperidol decanoate. *Ann Pharmacother* 1995; 29: 663–6.

Effects on lipid metabolism. Most antipsychotics are associated with hyperlipidaemia. A review[1] found evidence of a higher risk of hyperlipidaemia in patients receiving low-potency classical antipsychotics, such as chlorpromazine and thioridazine, or the atypical antipsychotics, clozapine, olanzapine, and quetiapine. High-potency classical antipsychotics, such as haloperidol, and the atypical antipsychotics aripiprazole, risperidone, and ziprasidone, appeared to be associated with a lower risk of hyperlipidaemia. Possible mechanisms for dyslipidaemia associated with antipsychotic therapy include the development of glucose intolerance, weight gain, and dietary changes. For further details, see Effects on Body-weight under Adverse Effects of Clozapine, p. 1059.1 and Effects on Body-weight, p. 1047.3.

1. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res* 2004; 70: 1–17.

Effects on the liver. Chlorpromazine and other phenothiazines may cause hepatocanalicular cholestasis often with hepatocyte damage suggestive of immunological liver injury.[1] Only a small number of patients taking the drug are affected and the onset is usually in the first 4 weeks of therapy. The drug or one of its metabolites may induce alteration in the liver-cell membrane so that it becomes antigenic; there is also good evidence for direct hepatotoxicity related to the production of free drug radical. There may be an individual idiosyncrasy in the metabolism of chlorpromazine and in the production of these radicals. A study has suggested that patients who have poor sulfoxidation status combined with unimpaired hydroxylation capacity may be most likely to develop jaundice with chlorpromazine.[2]

A preliminary study[3] showing a high incidence of gallstones in psychiatric inpatients in Japan found a correlation between the presence of gallstones and the duration of illness and use of antipsychotics. It was speculated that gallstones could be a consequence of phenothiazine-induced cholestasis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; II: 440–4.
2. Watson RGP, *et al.* A proposed mechanism for chlorpromazine jaundice—defective hepatic sulphoxidation combined with rapid hydroxylation. *J Hepatol* 1988; 7: 72–8.
3. Fukuzako H, *et al.* Ultrasonography detected a higher incidence of gallstones in psychiatric inpatients. *Acta Psychiatr Scand* 1991; 84: 83–5.

Effects on sexual function. The phenothiazines can cause both impotence and ejaculatory dysfunction.[1] Thioridazine has been frequently implicated, and in an early report 60% of 57 male patients taking the drug reported sexual dysfunction compared with 25% of 64 men taking other antipsychotics.[2] There are also several reports of priapism with phenothiazines;[1,3-5] alpha-adrenoceptor blocking properties of these compounds may be partly responsible. Male sexual dysfunction, including priapism, has been reported only rarely with other classical antipsychotics such as the butyrophenones, diphenylbutylpiperidines, and thioxanthenes.[6] Priapism has also been reported with clozapine[7] and other atypical antipsychotics. The effects of antipsychotics on female sexual function are less well studied. Orgasmic dysfunction has been reported with thioridazine, trifluoperazine, and fluphenazine.[8]

The effects of hyperprolactinaemia (see Effects on Endocrine Function, p. 1048.2) on sexual function are described on p. 2252.2.

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 23–42.
2. Kotin J, *et al.* Thioridazine and sexual dysfunction. *Am J Psychiatry* 1976; 133: 82–5.
3. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; 4: 46–58.
4. Chan J, *et al.* Perphenazine-induced priapism. *DICP Ann Pharmacother* 1990; 24: 246–9.
5. Salado J, *et al.* Priapism associated with zuclopenthixol. *Ann Pharmacother* 2002; 36: 1016–18.
6. Fabian J-L. Psychotropic medications and priapism. *Am J Psychiatry* 1993; 150: 349–50.
7. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; 55: 315–19.
8. Segraves RT. Psychiatric drugs and inhibited female orgasm. *J Sex Marital Ther* 1988; 14: 202–7.

Effects on the skin. *DEPOT INJECTION.* Of 217 patients given a combined total of 2354 depot antipsychotic injections 42 (19.4%) had local problems at the site of injection; 18 (8.3%) had chronic complications and 30 (13.8%) acute reactions.[1] Acute problems reported included 31 episodes of unusual pain, 21 of bleeding or haematoma, 19 of clinically important leakage of drug from injection site, 11 of acute inflammatory indurations, and 2 of transient nodules. Complications were more common in patients receiving concentrated preparations, higher doses, weekly injections, haloperidol decanoate or zuclopenthixol decanoate, and injection volumes greater than 1 mL and in those treated for more than 5 years. Chronic reactions were more common in patients aged over 50 years.

1. Hay J. Complications at site of injection of depot neuroleptics. *BMJ* 1995; 311: 421.

PHOTOSENSITIVITY. Testing in 7 subjects taking chlorpromazine revealed that photosensitivity reactions manifested mainly as immediate erythema and that sensitivity was primarily to light in the long ultraviolet (UVA) and visible wavebands. Sensitivity to UVB was normal.[1]

The incidence of photosensitivity reactions to chlorpromazine has been given as 3%. However, a higher incidence of 16 to 25% has also been reported.[2]

See also Effects on the Eyes, p. 1048.3.

1. Ferguson J, *et al.* Further clinical and investigative studies of chlorpromazine photosensitivity. *Br J Dermatol* 1986; 115 (suppl 30): 35.
2. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; 14: 252–9.

PIGMENTATION. The pigment found in the skin of patients treated with chlorpromazine was considered[1] to be a chlorpromazine-melanin polymer formed in a light-catalysed anaerobic reaction. Hydrogen chloride liberated during the reaction could account for the skin irritation. Intracutaneous injection of a preparation of the polymer into 2 subjects produced a bluish-purple discoloration which faded in 3 days.

1. Huang CL, Sands FL. Effect of ultraviolet irradiation on chlorpromazine II: anaerobic condition. *J Pharm Sci* 1967; 56: 259–64.

Extrapyramidal disorders. Antipsychotics and several other drugs, including antiemetics such as metoclopramide and some antidepressants, can produce a range of dyskinesias or involuntary movement disorders involving the extrapyramidal motor system, including parkinsonism, akathisia, acute dystonia, and chronic tardive dyskinesia.[1-4] Such reactions are a major problem in the clinical management of patients receiving antipsychotics. Reactions of this type can occur with any antipsychotic, but (excluding tardive dyskinesia) are particularly prominent during treatment with high-potency drugs such as the tricyclic piperazines and butyrophenones. Antipsychotics such as clozapine carry a low risk of extrapyramidal effects and are therefore described as atypical antipsychotics. The incidence of tardive dyskinesia does appear to be minimal with clozapine, although there is less evidence for other atypical antipsychotics (p. 1060.2; but see also below).

Of 2811 patients studied[5] in the first few months of therapy with prochlorperazine (a drug with a high propensity to cause extrapyramidal reactions), 57 reported adverse effects, 16 of which involved the extrapyramidal system. There were 4 dystonic-dyskinesic reactions (an incidence of 1 in 464 and 1 in 707 for patients aged under and over 30 years respectively), 9 reports of parkinsonism (under 60 years, 1 in 1555; over 60 years, 1 in 159), and 3 reports of akathisia (1 in 562).

One explanation of extrapyramidal disorders is an imbalance between dopaminergic and cholinergic systems in the brain. However, this simple model fails to explain the co-existence of a variety of extrapyramidal effects, and several alternative mechanisms have been proposed.[2,6] Hypotheses based on interactions between different dopamine receptor types may help to explain the decreased tendency of some antipsychotics to induce these reactions (see Action under Uses and Administration, p. 1046.1).

1. CSM/MCA. Drug-induced extrapyramidal reactions. *Current Problems* 1994; 20: 15–16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20156328RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
2. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; 47: 575–604.
3. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *Am J Health-Syst Pharm* 1997; 54: 2461–77.
4. Jiménez-Jiménez FJ, *et al.* Drug-induced movement disorders. *Drug Safety* 1997; 16: 180–204.
5. Bateman DN, *et al.* Extrapyramidal reactions to metoclopramide and prochlorperazine. *Q J Med* 1989; 71: 307–11.
6. Ereshefsky L, *et al.* Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; 9: 682–707.

AKATHISIA. Akathisia is a condition of mental and motor restlessness in which there is an urge to move about constantly and an inability to sit or stand still. It is the most common motor adverse effect of treatment with antipsychotics.[1] Acute akathisia is dose-dependent, usually develops within a few days of beginning treatment or after a rapid increase in dose, and usually improves if the drug is stopped or the dose reduced. *Antimuscarinic antiparkinsonian drugs* appear to provide only limited benefit, although success may be more likely in patients with concomitant parkinsonism. A low dose of a *beta blocker* such as *propranolol* (although good evidence is lacking[2]) or a *benzodiazepine*[3] may be helpful. Improvement has also been reported with *clonidine* and *amantadine* but the usefulness of these drugs may be limited by adverse effects or development of tolerance, respectively. The tardive form, like tardive dyskinesia (see below), which appears after several months of treatment, does not respond to antimuscarinics and is difficult to treat.

1. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Safety* 2000; 22: 73–81.
2. Barnes TRE, *et al.* Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).
3. Resende Lima A *et al.* Benzodiazepines for neuroleptic-induced acute akathisia. *Available in The Cochrane Database of Systematic Reviews;* Issue 4. Chichester: John Wiley; 1999 (accessed 15/05/09).

DYSTONIA. Acute dystonic reactions, which mainly affect the muscles of the face, neck, and trunk and include jaw clenching (trismus), torticollis, and oculogyric crisis are reported to occur in up to 10% of patients taking antipsychotics. Laryngeal dystonia is rare, but potentially fatal.[1] Dystonias usually occur within the first few days of treatment or after a dosage increase but may also develop on withdrawal. They are transitory, and are most common in children and young adults. Dystonic reactions may be controlled by *antimuscarinics* such as *biperiden* or *procyclidine*, or by *antihistamines* such as *diphenhydramine* or *promethazine*.[2] *Benzodiazepines* such as *diazepam* can also be used. Prophylactic antimuscarinics can prevent the development of dystonias, but routine use is not recommended as not all patients require them and tardive dyskinesia may be unmasked or worsened (see below); such a strategy should probably be reserved for short-term use in those at high risk of developing dystonic reactions, such as young adults starting treatment with high-potency antipsychotics or in patients with a history of drug-induced dystonias.[3,4] Some patients may develop tardive dystonia. A range of drugs has been tried in this condition but without consistent benefit.[5]

1. Koek RJ, Pi EH. Acute laryngeal dystonic reactions to neuroleptics. *Psychosomatics* 1989; 30: 359–64.
2. van Harten PN, *et al.* Acute dystonia induced by drug treatment. *BMJ* 1999; 319: 623–6.
3. WHO. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment: a consensus statement. *Br J Psychiatry* 1990; 156: 412.
4. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; 156: 413–14.
5. Raja M. Managing antipsychotic-induced acute and tardive dystonia. *Drug Safety* 1998; 19: 57–72.

PARKINSONISM. Parkinsonism, often indistinguishable from idiopathic Parkinson's disease (p. 889.1), may develop during therapy with antipsychotics, usually after the first few weeks or months of treatment. It is generally stated to be more common in adults and the elderly, although a retrospective study with haloperidol found an inverse relationship between drug-induced parkinsonism and age.[1] This parkinsonism is generally reversible on drug withdrawal or dose reduction, and may sometimes disappear gradually despite continued drug therapy. *Antimuscarinic antiparkinsonian* drugs are used to suppress the symptoms of parkinsonism.[2] However, they are often minimally effective and commonly cause adverse effects. Routine use for prophylaxis is not recommended because of the risk of unmasking or exacerbating tardive dyskinesia (see below). *Amantadine* is an alternative to the antimuscarinics.[2]

1. Moleman P, *et al.* Relationship between age and incidence of parkinsonism in psychiatric patients treated with haloperidol. *Am J Psychiatry* 1986; 143: 232–4.
2. Mamo DC, *et al.* Managing antipsychotic-induced parkinsonism. *Drug Safety* 1999; 20: 269–75.

TARDIVE DYSKINESIA. The central feature of tardive dyskinesia is orofacial dyskinesia characterised by protrusion of the tongue ('fly catching'), lipsmacking, sucking, lateral chewing, and pouting of the lips and cheeks. The trunk and limbs also become involved with choreiform movements such as repetitive 'piano-playing' hand movements, shoulder shrugging, foot tapping, or rocking movements. The prevalence of tardive dyskinesia among those receiving antipsychotics varies widely but up to 60% of patients may develop symptoms. In most cases the condition is mild and not progressive and tends to wax and wane. Although tardive dyskinesia usually develops after many years of antipsychotic therapy no clear correlation has been shown between development of the condition and the length of drug treatment or the type and class of drug. However, *clozapine* does not appear to be associated with the condition (but see below) and in some cases use has resulted in improvement of established tardive dyskinesia (see Schizophrenia under Clozapine, p. 1058.2). Whether other atypical antipsychotics also have a lower incidence of tardive dyskinesia is unknown. Early data suggested that this may be the case;[1-3] a more recent cohort study[4] concluded that the risk with atypical antipsychotics (excluding clozapine) is more than half that with classical antipsychotics. Perhaps surprisingly, this study also found that there was a non-significant increase in the risk of tardive dyskinesia with clozapine when compared with clas-

sical antipsychotics. However, it was not clear whether this was an actual increase in risk with clozapine or if clozapine-treated patients were at a greater risk of illness-related dyskinesia. Symptoms of tardive dyskinesia often develop after stopping the antipsychotic or after dose reduction. Risk factors include old age, female sex, affective disorder, schizophrenia characterised by negative symptoms, and organic brain damage.

Suggested causes of tardive dyskinesia include dopaminergic overactivity, imbalance between dopaminergic and cholinergic activity, supersensitivity of postsynaptic dopamine receptors, presynaptic catecholaminergic hyperfunction, and alterations of the gamma-aminobutyric acid (GABA) system.

Options in the management of tardive dyskinesia include attempts at treatment while maintaining antipsychotic therapy, or withdrawal of antimuscarinic therapy, and either withdrawal of the antipsychotic or reduction of the dosage to the minimum required or transfer to an atypical antipsychotic.

Although many drugs have been tried in the **treatment** of tardive dyskinesia there have been relatively few double-blind studies. Reviews of tardive dyskinesia[1,5-7] have concluded that there appeared to be no reliable or safe treatment. Overall, classical antipsychotics appeared to be the most effective in masking symptoms of tardive dyskinesia but tolerance may develop and a worsening of the underlying pathophysiology by antipsychotics had to be assumed on theoretical grounds. Other drugs with antidopaminergic actions that were probably of comparable efficacy included *reserpine, oxypertine, tetrabenazine,* and *metirosine*. The next most effective drugs were considered to be noradrenergic antagonists such as *clonidine*. Some encouraging results had also been obtained with GABAergic drugs such as the *benzodiazepines, baclofen, valproate,* and *vigabatrin*, although systematic reviews of studies of some GABAergic drugs[8] including benzodiazepines[9] found the evidence inconclusive and/or unconvincing. The efficacy of cholinergics could not be confirmed.[10,11] Dopaminergics and antimuscarinics mostly exacerbated symptoms but others[12] had commented that there was no convincing evidence that long-term use of antimuscarinics increased the risk of developing the condition. Other drugs whose value is unclear include *vitamin E*[13] and some calcium-channel blockers.[14]

Withdrawal of the causative drug usually worsens the condition although symptoms often diminish or disappear over a period of weeks or sometimes a year or so. Success is most likely in younger patients. During withdrawal, drugs such as *diazepam* or *clonazepam* may be given to alleviate symptoms. Although classical antipsychotics are effective, their routine use to suppress symptoms is not recommended but they may be required for acute distressing or life-threatening reactions or in chronic tardive dyskinesia unresponsive to other treatment. In extremely severe resistant cases some have used an antipsychotic with *valproate* or *carbamazepine* or *reserpine* with *metirosine*.

In view of the unsatisfactory management of tardive dyskinesia, emphasis is placed on its **prevention**. Antipsychotics should be prescribed only when clearly indicated, should be given in the minimum dose, and continued only when there is evidence of benefit. Although drug holidays have been suggested for reducing the risk of tardive dyskinesia, the limited evidence indicates that interruptions in drug treatment may increase the risk of both persistent dyskinesia and psychotic relapse.[15] Increasing the dose of antipsychotic generally improves the condition, but only temporarily.

1. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res* 1999; 35 (suppl): S61–S66.
2. Kane JM. Tardive dyskinesia in affective disorders. *J Clin Psychiatry* 1999; 60 (suppl 5): 43–7.
3. Llorca P-M, *et al.* Tardive dyskinesias and antipsychotics: a review. *Eur Psychiatry* 2002; 17: 129–38.
4. Woods SW, *et al.* Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study. *J Clin Psychiatry* 2010; 71: 463–74.
5. Haag H, *et al.*, eds. Tardive Dyskinesia. *WHO Expert Series on Biological Psychiatry Volume 1*. Seattle: Hogrefe & Huber, 1992.
6. Egan MF, *et al.* Treatment of tardive dyskinesia. *Schizophr Bull* 1997; 23: 583–609.
7. Najib J. Tardive dyskinesia: a review and current treatment options. *Am J Ther* 1999; 6: 51–60.
8. Rathbone J, *et al.* Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 12/08/08).
9. Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).
10. Tammenmaa I, *et al.* Cholinergic medication for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/08/08).
11. Tammenmaa IA, *et al.* Systematic review of cholinergic drugs for neuroleptic-induced tardive dyskinesia: a meta-analysis of randomized controlled trials. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28: 1099–1107.
12. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; 156: 413–14.
13. McGrath J, Soares-Weiser K. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 21/08/08).
14. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/05).
15. Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 12/05/06).

Neuroleptic malignant syndrome. The neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to some drugs including antipsychotics and other dopamine antagonists such as metoclopramide. The clinical **features** of the classic syndrome are usually considered to include hyperthermia, severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction, and altered levels of consciousness. Skeletal muscle damage may occur and the resulting myoglobinuria may lead to renal failure. However, there appear to be no universal criteria for diagnosis. Some believe the classic syndrome to be the extreme of a range of effects associated with antipsychotics and have introduced the concept of milder variants or incomplete forms. Others consider it to be a rare idiosyncratic reaction and suggest that the term neuroleptic malignant syndrome should be reserved for the full-blown reaction. Consequently, estimates of the **incidence** vary greatly and recent estimates have ranged from 0.02 to 2.5%. The mortality rate has been substantial; although it has decreased over the years with improved diagnosis and management, this may also be due to the detection and inclusion of the milder or incomplete variants. Possible risk factors include dehydration, pre-existing organic brain disease, and a history of a previous episode; young males have also been reported to be particularly susceptible.

The **pathogenesis** of NMS is still unclear. Blockade of dopaminergic receptors in the corpus striatum is thought to cause muscular contraction and rigidity generating heat while blockade of dopaminergic receptors in the hypothalamus leads to impaired heat dissipation. Peripheral mechanisms such as vasomotor paralysis may also play a role. Also a syndrome resembling NMS has been seen after withdrawal of treatment with dopamine agonists such as levodopa (see p. 906.2). Symptoms develop rapidly over 24 to 72 hours and may occur days to months after starting antipsychotic medication or increase in dosage, but no consistent correlation with dosage or length of therapy has been found. Symptoms may last for up to 14 days after stopping oral antipsychotics, or for up to 4 weeks after stopping depot preparations. All antipsychotics are capable of inducing NMS; depot preparations may, however, be associated with prolonged recovery once it develops, and hence a higher mortality rate. Use with lithium carbonate or antimuscarinics may increase the likelihood of developing the syndrome.

Antipsychotic medication should be withdrawn immediately once the diagnosis of the classic syndrome is made; this should be followed by symptomatic and supportive **therapy** including cooling measures, correction of dehydration, and treatment of cardiovascular, respiratory, and renal complications. Whether antipsychotics should be withdrawn from patients with mild attacks and how they should be managed is a matter of debate.

The efficacy of specific drug therapy remains to be proven, and justification for use is based mainly on case reports.

- *Dantrolene* was first used because of its efficacy in malignant hyperthermia. It has a direct action on skeletal muscle and may be particularly effective for the reversal of hyperthermia of muscle origin.
- In contrast, dopaminergic agonists may resolve hyperthermia of central origin, restoring dopaminergic transmission and hence alleviating extrapyramidal symptoms. There have been isolated reports of success with *amantadine* and *levodopa* but *bromocriptine* is generally preferred. Any underlying psychosis may, however, be aggravated by dopaminergic drugs.
- Since dantrolene and dopaminergics act in different ways a combination of the two might be useful, but any advantage is unproven.
- *Antimuscarinics* are generally considered to be of little use and may aggravate the associated hyperthermia.
- *Benzodiazepines* may be used for sedation in agitated patients and may be of use against concomitant catatonia. ECT may be an alternative in refractory cases of NMS or when catatonic symptoms are present.

Re-introduction of antipsychotic therapy may be possible but is not always successful and extreme caution is advised. It has been recommended that a gap of at least 5 to 14 days should be left after resolution of the symptoms before attempting re-introduction.

References.

1. Wells AJ, *et al.* Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. *Drug Intell Clin Pharm* 1988; 22: 475–80.
2. Bristow MF, Kohen D. How "malignant" is the neuroleptic malignant syndrome? *BMJ* 1993; 307: 1223–4.
3. Kornhuber J, Weller M. Neuroleptic malignant syndrome. *Curr Opin Neurol* 1994; 7: 353–7.
4. Velamoor VR, *et al.* Management of suspected neuroleptic malignant syndrome. *Can J Psychiatry* 1995; 40: 545–50.
5. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; 47: 575–604.
6. Bristow MF, Kohen D. Neuroleptic malignant syndrome. *Br J Hosp Med* 1996; 55: 517–20.
7. Velamoor VR. Neuroleptic malignant syndrome: recognition, prevention and management. *Drug Safety* 1998; 19: 73–82.
8. Adnet P, *et al.* Neuroleptic malignant syndrome. *Br J Anaesth* 2000; 85: 129–35.
9. Strawn JR, *et al.* Neuroleptic malignant syndrome. *Am J Psychiatry* 2007; 164: 870–6.

Withdrawal. Stopping treatment with an antipsychotic abruptly may produce withdrawal symptoms, the most common of which are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation.[1] Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days. They are more severe and frequent when antimuscarinics are stopped simultaneously.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; 10: 103–14.

Treatment of Adverse Effects

After an overdose of chlorpromazine or other phenothiazines, patients should be managed with intensive symptomatic and supportive therapy. Activated charcoal should be given orally if a potentially toxic amount of the phenothiazine has been ingested within 1 hour of presentation, provided that the airway can be protected; the benefit of gastric decontamination is uncertain. Dialysis is of little or no value in poisoning by phenothiazines.

Hypotension should be corrected by raising the patient's legs and by giving intravenous fluids. Drugs with pronounced alpha-adrenergic activity, such as noradrenaline, or high-dose dopamine may be beneficial where hypotension is thought to be mainly due to decreased systemic vascular resistance. Central venous pressure monitoring should be considered in refractory cases. If a vasoconstrictor is considered necessary in the management of phenothiazine-induced hypotension the use of adrenaline or other sympathomimetics with high beta-adrenergic agonist properties should be avoided since the alpha-blocking effects of phenothiazines may impair the usual alpha-mediated vasoconstriction of these drugs, resulting in unopposed beta-adrenergic stimulation and increased hypotension.

The treatment of neuroleptic malignant syndrome and the difficulties of treating extrapyramidal adverse effects, especially tardive dyskinesia, are discussed above and on p. 1049.2, respectively.

Precautions

Chlorpromazine and other phenothiazines are contra-indicated in patients with pre-existing CNS depression or coma, bone-marrow suppression, phaeochromocytoma, or prolactin-dependent tumours. They should be used with caution or not at all in patients with impaired liver, kidney, cardiovascular, cerebrovascular, and respiratory function and in those with angle-closure glaucoma, a history of jaundice, parkinsonism, diabetes mellitus, hypothyroidism, myasthenia gravis, paralytic ileus, prostatic hyperplasia, or urinary retention. Care is required in patients with epilepsy or a history of seizures as phenothiazines may lower the seizure threshold. Debilitated patients may be more prone to the adverse effects of phenothiazines as may the elderly, especially those with dementia. For precautions of phenothiazines in pregnancy, see p. 1051.3.

The sedative effects of phenothiazines are most marked in the first few days of treatment; affected patients should not drive or operate machinery.

The effects of phenothiazines on the vomiting centre may mask the symptoms of overdosage of other drugs, or of disorders such as gastrointestinal obstruction. Use at extremes of temperature may be hazardous since body temperature regulation is impaired by phenothiazines.

Regular eye examinations are advisable for patients receiving long-term phenothiazine therapy and avoidance of undue exposure to direct sunlight is recommended. Phenothiazines should be used with caution in the presence of acute infection or leucopenia. Blood counts are advised if the patient develops an unexplained infection or fever.

Patients should remain supine for at least 30 minutes after parenteral doses of chlorpromazine; blood pressure should be monitored.

Abrupt withdrawal of phenothiazine therapy is best avoided.

AIDS. Isolated reports[1,2] have suggested that patients with AIDS may be particularly susceptible to antipsychotic-induced extrapyramidal effects.

1. Hollander H, *et al.* Extrapyramidal symptoms in AIDS patients given low-dose metoclopramide or chlorpromazine. *Lancet* 1985; ii: 1186.
2. Edelstein H, Knight RT. Severe parkinsonism in two AIDS patients taking prochlorperazine. *Lancet* 1987; ii: 341–2.

Asthma. Findings of a retrospective case-control study[1] appeared to indicate that asthmatic patients given antipsychotics were at an increased risk of death or near death from asthma.

1. Joseph KS, *et al.* Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ* 1996; 312: 79–82.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of chlorpromazine by mothers during breast feeding may be of concern, since there have been reports of galactorrhoea in the mother and of drowsiness, lethargy, and declines in developmental scores in the infant. The *BNF* considers that the use of antipsychotics such as chlorpromazine should be avoided by breast-feeding mothers unless absolutely necessary.

Chlorpromazine was detected[2] in all milk samples from 4 women at concentrations ranging from 7 to 98 nanograms/mL. Two of the women breastfed their infants, but one infant showed no effects while the other was noted to be drowsy and lethargic; milk-chlorpromazine concentrations were 7 and 92 nanograms/mL, respectively.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/10/04)
2. Wiles DH, *et al.* Chlorpromazine levels in plasma and milk of nursing mothers. *Br J Clin Pharmacol* 1978; 5: 272–3.

Children. Few phenothiazines are recommended for use in children; in particular there have been concerns about the use of phenothiazine derivatives in infants (see Sudden Infant Death Syndrome, p. 639.1). For reference to the use of chlorpromazine in infants suffering neonatal abstinence syndrome see Substance Dependence, Opioids, under Uses and Administration, p. 1047.1. For other uses in children see also Administration in Children, p. 1046.2.

References.

1. Dyer KS, Woolf AD. Use of phenothiazines as sedatives in children: what are the risks? *Drug Safety* 1999; 21: 81–90.

Contact sensitisation. The *BNF* warns that because of the risk of contact sensitisation, health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

Driving. While psychotic disorders probably adversely affect driving skill, treatment with antipsychotics can also be hazardous, although patients may be safer drivers with medication than without. Impairment of performance is largely related to sedative and extrapyramidal effects. In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. During an acute psychotic illness, or an episode of mania or hypomania, driving should cease. After an isolated episode, re-licensing can be considered provided the patient has remained well and stable for at least 3 months, is compliant with treatment, and has regained insight; in addition, the patient should be free from any adverse effects of medication that would impair driving. If there have been 4 or more episodes of mood swing within the previous 12 months, at least 6 months of stability will be required before re-licensing can be considered. Drivers of heavy goods and public service vehicles are normally required to be well and stable for 3 years before driving can resume.[1]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 25/11/13)

The elderly. The risk of *hip fracture* has been reported to be increased in elderly patients given antipsychotics. A large case-control study in patients over 65 found that current users of antipsychotics had a twofold increase in the risk of hip fractures.[1] The effect was dose-related and the increased risk was similar for chlorpromazine, haloperidol, and thioridazine. It was suggested that antipsychotic-induced sedation or orthostatic hypotension could increase the risk of falls in elderly persons. A study in 12 schizophrenic patients receiving antipsychotics plus other drugs such as antimuscarinics or benzodiazepines has suggested that long-term treatment with antipsychotics may decrease bone mineralisation.[2] A later study suggested that any increased risk of falls might be due to an effect of antipsychotics on balance as thioridazine was found to increase sway in elderly but not young subjects.[3] A meta-analysis of 98 studies[4] concluded that there was a moderate and clinically significant increase in the risk of fractures with the use of most classes of psychotropic drugs, including antipsychotics. However, the evidence from these studies was based solely on observational data, with minimal adjustment for confounders, and potential for publication bias.

A large case-control study[5] found the risk of community-acquired *pneumonia* to be increased in patients aged 65 years and over who were current users of either classical or atypical antipsychotics. The risk was dose-dependent and occurred soon after beginning treatment.

The use of antipsychotics to manage behavioural complications of *dementia* may increase the rate of cognitive decline.[6,7] Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotic drugs,[8,9] and the reaction can be extremely serious, even fatal. If these drugs are to be used in elderly patients with dementia, then very low doses should be used, and special care should be taken if the dementia is suspected to be of the Lewy-body type since sudden life-threatening deterioration may occur.[10] Depot preparations should not be used and, since dopamine D_2 receptors may be involved, it has been suggested that consideration could be given to using an antipsychotic such as clozapine that does not principally antagonise those receptors;[9] however, the use of atypical antipsychotics in such patients is not without its risk and there is evidence of an increased death rate with their use (see under Risperidone, p. 1105.1).

An *increased risk of death* has also been noted in elderly patients given classical antipsychotics. Retrospective cohort studies,[11,12] involving around 60 000 patients given atypical or classical antipsychotics, found that classical antipsychotics were at least as likely as the atypicals to increase the risk of death in the elderly. The authors also suggested that the greatest increase in risk occurred soon after starting therapy and with higher doses of classical antipsychotics. A similar risk of death with use of classical antipsychotics was also seen in a large retrospective population-based study[13] in elderly patients with dementia when compared with that seen with use of atypicals in this patient group. On review of 2 of these studies,[12,13] the FDA concluded that both classical and atypical antipsychotics were associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.[14] However, methodological limitations precluded any conclusion that classical antipsychotics have a greater mortality risk than atypical antipsychotics.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p. 1030.2.

1. Ray WA, *et al.* Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987; 316: 363–9.
2. Higuchi T, *et al.* Certain neuroleptics reduce bone mineralization in schizophrenic patients. *Neuropsychobiology* 1987; 18: 185–8.
3. Liu Y, *et al.* Comparative clinical effects of thioridazine (THD) on fall risk on young and elderly subjects. *Clin Pharmacol Ther* 1995; 57: 200.
4. Takkouche B, *et al.* Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Safety* 2007; 30: 171–84.
5. Trifirò G, *et al.* Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med* 2010; 152: 418–25.
6. McShane R, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ* 1997; 314: 266–70.
7. Holmes C, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Carriers of apolipoprotein E ε 4 allele seem particularly susceptible to their effects. *BMJ* 1997; 314: 1411.
8. McKeith I, *et al.* Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* 1992; 305: 673–8.
9. Piggott MA, *et al.* DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* 1994; 343: 1044–5. Correction. *ibid.*; 1170. [Title: Dopamine D2 receptors in demented patients with severe neuroleptic sensitivity.]
10. CSM/MCA. Neuroleptic sensitivity in patients with dementia. *Current Problems* 1994; 20: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 30/05/06)
11. Wang PS, *et al.* Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; 353: 2335–41.
12. Schneeweiss S, *et al.* Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *Can Med Assoc J* 2007; 176: 627–32. Correction. *ibid.*; 1613.
13. Gill SS, *et al.* Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; 146: 775–86.
14. FDA. Information for healthcare professionals: conventional antipsychotics (issued 16th June, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm (accessed 26/07/10)

Epilepsy. See Convulsions under Adverse Effects, p. 1047.3.

Folic acid deficiency. Concentrations of folate in serum and erythrocytes were reduced in 15 patients receiving long-term treatment with chlorpromazine or thioridazine.[1] All the patients had significant induction of hepatic microsomal enzymes. It was suggested that folate deficiency due to the induction of microsomal enzymes might subsequently limit enzyme induction and hence reduce drug metabolism, which could lead to symptoms of toxicity in patients apparently stabilised for several years. The dietary intake of patients on long-term treatment with enzyme-inducing drugs might be inadequate.

1. Labadarios D, *et al.* The effects of chronic drug administration on hepatic enzyme induction and folate metabolism. *Br J Clin Pharmacol* 1978; 5: 167–73.

Hypoparathyroidism. There have been rare reports[1,2] of acute dystonic reactions associated with the use of phenothiazines in patients with untreated hypoparathyroidism. Caution was recommended in giving phenothiazine derivatives to patients with hypoparathyroidism and it was suggested that any acute reaction to such a drug should prompt investigation for some form of latent tetany.

1. Schaaf M, Payne CA. Dystonic reactions to prochlorperazine in hypoparathyroidism. *N Engl J Med* 1966; 275: 991–5.
2. Gur H, *et al.* Acute dystonic reaction to methotrimeprazine in hypoparathyroidism. *Ann Pharmacother* 1996; 30: 957–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorpromazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pregnancy. Licensed product information generally does not recommend the use of phenothiazines in late pregnancy; such use may be associated with intoxication of the neonate. Chlorpromazine may prolong labour and should be withheld until the cervix is dilated 3 to 4 cm. Overall, however, it has been suggested[1] that the criteria for the selection of an antipsychotic for use in pregnant women do not differ from those used in nonpregnant women. It was also concluded that the benefits of continuing antipsychotic treatment at the minimum effective dose would usually outweigh any risks to the fetus.

A review[2] of the use of phenothiazines in pregnancy concluded that there was no clear evidence that these drugs caused a significant increase in fetal malformations. Nevertheless it was considered advisable that if pregnant patients required such treatment, then a single phenothiazine should be used and that it should be one of the established drugs.

A subsequent review[3] of the literature reported that women with schizophrenia are generally at increased risk for poor obstetric outcomes including preterm delivery, low birth-weight, and neonates who are small for their gestational age. It was also considered that there was an increased risk of congenital malformation when the fetus was exposed to phenothiazines during weeks 4 to 10 of gestation but this conclusion and the methods used to select the data to review have been criticised.[4]

See also p. 614.2 for the use of phenothiazines as antiemetics during pregnancy.

1. Trixler M, Tényi T. Antipsychotic use in pregnancy: what are the best treatment options? *Drug Safety* 1997; 16: 403–10.
2. McElhatton PR. The use of phenothiazines during pregnancy and lactation. *Reprod Toxicol* 1992; 6: 475–90.
3. Patton SW, *et al.* Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can J Psychiatry* 2002; 47: 959–65.
4. Levinson A. Review: women with schizophrenia have poorer pregnancy outcomes than other women, but it is unclear whether antipsychotic medications affect their infants. *Evid Based Ment Health* 2003; 6: 89.

Renal impairment. Although there do not seem to be specific indications for dosage adjustment of phenothiazines in renal impairment, the *BNF* considers that cerebral sensitivity to antipsychotics may be increased in severe impairment. Phenothiazine-induced toxic psychosis occurred in 4 patients with chronic renal failure who had been given chlorpromazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; 10: 191–5.

Interactions

The most common interactions encountered with phenothiazines such as chlorpromazine result from use with drugs that have similar pharmacological actions. Symptoms of CNS depression may be enhanced by other drugs with CNS-depressant properties including alcohol, general anaesthetics, hypnotics, anxiolytics, and opioids. When given with other drugs that produce orthostatic hypotension, dosage adjustments may be necessary. However, it should be noted that phenothiazines have been reported to reduce the antihypertensive action of guanethidine and other adrenergic neurone blockers. As many phenothiazines possess antimuscarinic actions they can potentiate the adverse effects of other drugs with antimuscarinic actions, including tricyclic antidepressants and the antimuscarinic antiparkinsonian drugs that may be given to treat phenothiazine-induced extrapyramidal effects. In theory, antipsychotics with dopamine-blocking activity and dopaminergic drugs such as those used to treat parkinson-

ism may be mutually antagonistic. Use with metoclopramide may increase the risk of antipsychotic-induced extrapyramidal effects.

There is an increased risk of arrhythmias when antipsychotics are used with drugs that prolong the QT interval, including certain antiarrhythmics, other antipsychotics, some non-sedating antihistamines, antimalarials, and cisapride; use with diuretics that cause electrolyte imbalance (particularly hypokalaemia) may also have the same effect. There is also an increased risk of arrhythmias when tricyclic antidepressants are used with antipsychotics that prolong the QT interval.

Because of an increased risk of seizures US licensed product information for chlorpromazine recommends withdrawal before the use of metrizamide for radiographic procedures.

Most interactions with antipsychotics are as a result of additive pharmacological effects.[1] Since tolerance develops to many of these adverse effects, interactions are likely to be most important in the early stages of combination therapy.

1. Livingston MG. Interactions that matter: 11 antipsychotic drugs. *Prescribers' J* 1987; 27(Dec): 26–9.

Alcohol. Phenothiazines may increase the CNS depressant effects of alcohol. There has been a report of akathisia and dystonia after consumption of alcohol by patients taking antipsychotics;[1] alcohol might lower the threshold of resistance to neurotoxic adverse effects.

1. Lutz EG. Neuroleptic-induced akathisia and dystonia triggered by alcohol. *JAMA* 1976; 236: 2422–3.

Antacids. Studies in 6 patients showed that chlorpromazine plasma concentrations were significantly lower after giving chlorpromazine with an *aluminium hydroxide* and *magnesium trisilicate* antacid gel (*Gelusil*) than after chlorpromazine alone.[1] *In-vitro* studies indicated that chlorpromazine was highly bound to the gel.

1. Fann WE, *et al.* Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J Clin Pharmacol* 1973; 13: 388–90.

Antiarrhythmics. There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with antiarrhythmics (especially *amiodarone, disopyramide, procainamide,* and *quinidine*) should be avoided. Use of haloperidol with amiodarone is also not recommended. A study[1] in healthy subjects has suggested that quinidine might increase plasma concentrations of haloperidol.

1. Young D, *et al.* Effect of quinidine on the interconversion kinetics between haloperidol and reduced haloperidol in humans: implications for the involvement of cytochrome P450IID6. *Eur J Clin Pharmacol* 1993; 44: 433–8.

Antibacterials. Seven schizophrenic patients whose antitubercular therapy included *rifampicin* (in addition to isoniazid, and in some cases also ethambutol) had lower serum concentrations of haloperidol compared with tuberculotic schizophrenic patients receiving no antimycobacterials and with non-tuberculotic schizophrenics.[1] Pharmacokinetic studies involving some of these patients indicated accelerated haloperidol clearance in the presence of rifampicin. Abnormally high serum-haloperidol concentrations occurred in 3 of 18 patients treated with *isoniazid* alone.

Black galactorrhoea occurred in a patient receiving *minocycline*, perphenazine, amitriptyline hydrochloride, and diphenhydramine hydrochloride.[2] Simultaneous occurrence of phenothiazine-induced galactorrhoea and tetracycline-induced pigmentation was considered responsible.

Sudden cardiac deaths have been reported[3] in patients given *clarithromycin* and pimozide. Elevated pimozide plasma concentrations were recorded after pretreatment with clarithromycin.[4] The manufacturer of pimozide has recommended that pimozide should not be used with macrolide antibacterials.

1. Takeda M, *et al.* Serum haloperidol levels of schizophrenics receiving treatment for tuberculosis. *Clin Neuropharmacol* 1986; 9: 386–97.
2. Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; 121: 417–18.
3. Plockhart DA, *et al.* A metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity. *Clin Pharmacol Ther* 1996; 59: 189.
4. Desta Z, *et al.* Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolisers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; 65: 10–20.

Anticoagulants. For reference to the effects of some antipsychotics on the activity of anticoagulants, see under Warfarin, p. 1533.1.

Antidepressants. Interactions between antipsychotics and *tricyclic antidepressants* are generally of two forms: additive pharmacological effects such as antimuscarinic effects or hypotension; or pharmacokinetic interactions. Although not commonly reported in the literature, additive antimuscarinic activity may be a significant risk especially in the elderly. Careful drug selection might help to prevent the development of serious adverse effects. Mutual inhibition of liver enzymes involved in the metabolism of both the antipsychotic and the tricyclic antidepressant might result in increased plasma concentrations of either drug. In one study,[1] addition of *nortriptyline* to chlorpromazine therapy produced an increase in plasma concentrations of chlorpromazine but this resulted in a paradoxical increase in agitation and tension.

There is an increased risk of arrhythmias when tricyclic antidepressants are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with tricyclic antidepressants should be avoided.

Increased serum concentrations of haloperidol have occurred when patients were also given *fluoxetine*,[2] *fluvoxamine*,[3] or *nefazodone*. Isolated reports[4-9] of extrapyramidal symptoms, psychoneuromotor syndrome, stupor, bradycardia, and urinary retention associated with use of fluoxetine with antipsychotics suggest that fluoxetine might exacerbate the adverse effects of antipsychotics or produce additive toxicity. Similar CNS effects have been noted in subjects given perphenazine and *paroxetine*.[10] There has also been an isolated report of a patient who complained of amenorrhoea and galactorrhoea after fluvoxamine was added to loxapine therapy.[11] Significant increases in the plasma concentrations of thioridazine have occurred after use with fluvoxamine.[12] Paroxetine may also inhibit the metabolism of thioridazine, resulting in increased thioridazine plasma concentrations; UK licensed product information for paroxetine contra-indicates their concomitant use. The US licensed product information for paroxetine states that giving paroxetine with pimozide was associated with a mean increase of 151% in the area under the concentration-time curve of pimozide and 62% in its mean peak plasma concentration. Due to the narrow therapeutic index of pimozide concomitant use of these 2 drugs is contra-indicated.

Combinations of antipsychotics and *lithium* should be used with care. Lithium can reduce plasma-chlorpromazine concentrations and there is a report of ventricular fibrillation on withdrawal of lithium from a patient also taking chlorpromazine. Chlorpromazine has also been reported to enhance the excretion of lithium. Neurotoxic or extrapyramidal symptoms have been reported rarely in patients taking antipsychotics and lithium; these may be atypical cases of lithium toxicity or neuroleptic malignant syndrome. The above issues are discussed in detail, and references given, on p. 431.3.

A patient on long-term trifluoperazine treatment developed neuroleptic malignant syndrome after a single dose of *venlafaxine*.[13] The authors noted that the manufacturers of venlafaxine have received a small number of similar reports after introduction of venlafaxine in patients receiving antipsychotics including molindone.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with phenothiazines.

1. Loga S, *et al.* Interaction of chlorpromazine and nortriptyline in patients with schizophrenia. *Clin Pharmacokinet* 1981; 6: 454–62.
2. Goff DC, *et al.* Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. *Am J Psychiatry* 1991; 148: 790–2.
3. Daniel DG, *et al.* Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* 1994; 14: 340–3.
4. Tate JL. Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine. *Am J Psychiatry* 1989; 146: 399–400.
5. Ahmed I, *et al.* Possible interaction between fluoxetine and pimozide causing sinus bradycardia. *Can J Psychiatry* 1993; 38: 62–3.
6. Ketai R. Interaction between fluoxetine and neuroleptics. *Am J Psychiatry* 1993; 150: 836–7.
7. Hansen-Grant S, *et al.* Fluoxetine-pimozide interaction. *Am J Psychiatry* 1993; 150: 1751–2.
8. D'Souza DC, *et al.* Precipitation of a psychoneuromotor syndrome by fluoxetine in a haloperidol-treated schizophrenic patient. *J Clin Psychopharmacol* 1994; 14: 361–3.
9. Benazzi F. Urinary retention with fluoxetine-haloperidol combination in a young patient. *Can J Psychiatry* 1996; 41: 606–7.
10. Özdemir V, *et al.* Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin Pharmacol Ther* 1997; 62: 334–47.
11. Jeffries J, *et al.* Amenorrhea and galactorrhea associated with fluvoxamine in a loxapine-treated patient. *J Clin Psychopharmacol* 1992; 12: 296–7.
12. Carrillo JA, *et al.* Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. *J Clin Psychopharmacol* 1999; 19: 494–9.
13. Nimmagadda SR, *et al.* Neuroleptic malignant syndrome after venlafaxine. *Lancet* 2000; 354: 289–90.

Antidiabetic drugs. Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance the dose of *oral hypoglycaemics* or of *insulin* may need to be increased in diabetics.

Antiepileptics. *Carbamazepine, phenobarbital,* and *phenytoin* are potent enzyme inducers and may decrease plasma concentrations of antipsychotics or their active metabolites when used together.[1-3] The clinical effect of any interaction has not been consistent; worsening, improvement, or no change in psychotic symptoms have all been noted. Delirium has been reported in a patient given haloperidol and carbamazepine.[4] Phenytoin might also exacerbate antipsychotic-induced dyskinesia.[7] Care should be taken when withdrawing enzyme-inducing antiepileptics as this may result in a rise in antipsychotic serum concentrations.[8]

The effect of antipsychotics on antiepileptic concentrations is discussed on p. 517.2 (carbamazepine) and p. 544.1 (phenytoin). It should also be remembered that antipsychotics may lower the seizure threshold.

1. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; 2: 197–208.
2. Linnoila M, *et al.* Effect of anticonvulsants on plasma haloperidol and thioridazine levels. *Am J Psychiatry* 1980; 137: 819–21.
3. Jann MW, *et al.* Effects of carbamazepine on plasma haloperidol levels. *Clin Psychopharmacol* 1985; 5: 106–9.
4. Arana GW, *et al.* Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? *Am J Psychiatry* 1986; 143: 650–1.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; 11: 296–301.
6. Kanter GL, *et al.* Case report of a possible interaction between neuroleptics and carbamazepine. *Am J Psychiatry* 1984; 141: 1101–2.
7. DeVeaugh-Geiss J. Aggravation of tardive dyskinesia by phenytoin. *N Engl J Med* 1978; 298: 457–8.
8. Jann MW, *et al.* Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* 1989; 28: 153–9.

Antihistamines. For the effect of a preparation containing *chlorphenamine maleate* and phenylpropanolamine hydrochloride on thioridazine, see Sympathomimetics (p. 1053.2). There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with antihistamines such as *astemizole* or *terfenadine* should be avoided.

Antihypertensives. For discussion of the interaction between phenothiazines and drugs with hypotensive properties, see Interactions, p. 1051.3. For a report of chlorpromazine enhancing the hyperglycaemic effect of *diazoxide*, see p. 1352.2. For reports of hypertension or dementia in patients given *methyldopa* and antipsychotics, see p. 1432.3.

Antimalarials. Pretreatment with single doses of *chloroquine sulfate, amodiaquine hydrochloride,* or *sulfadoxine with pyrimethamine* increased the plasma concentrations of chlorpromazine and 7-hydroxychlorpromazine, but not of chlorpromazine sulfoxide, in schizophrenic patients maintained on chlorpromazine.[1] The raised plasma concentrations appeared to be associated with a greater level of sedation.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of antipsychotics, and pimozide in particular, with antimalarials such as *halofantrine, mefloquine,* or *quinine* should be avoided. For the possible effects of the use of *quinidine* with antipsychotics see Antiarrhythmics, above.

1. Makanjuola ROA, *et al.* Effects of antimalarial agents on plasma levels of chlorpromazine and its metabolites in schizophrenic patients. *Trop Geogr Med* 1988; 40: 31–3.

Antimigraine drugs. A report[1] of a patient receiving loxapine who had a dystonic reaction within 15 minutes of subcutaneous *sumatriptan* suggests that these two drugs might interact or potentiate each other's adverse effects. However, the patient had a history of dystonic reactions associated with haloperidol and was receiving benzatropine prophylactically. Furthermore, the dose of loxapine had been increased 2 days before the event and this may have predisposed the patient to dystonia.

1. Garcia G, *et al.* Dystonic reaction associated with sumatriptan. *Ann Pharmacother* 1994; 28: 1199.

Antiparkinsonian drugs. Antiparkinsonian drugs are sometimes given with antipsychotics for the management of antipsychotic-induced adverse effects including extrapyramidal disorders (see under Adverse Effects, p. 1049.2). Theoretically, dopaminergics such as *levodopa* and *bromocriptine* might induce or exacerbate psychotic symptoms. A study in 18 subjects and review of the literature suggested that bromocriptine can be used safely in patients at risk of psychotic illness provided they are clinically stable and maintained on antipsychotics.[1] Conversely, antipsychotics might antagonise the effects of dopaminergics; diminished therapeutic effects of levodopa have been noted with several antipsychotics (see p. 907.3) and thioridazine has been reported to oppose the prolactin-lowering action of bromocriptine (see p. 899.1).

Additive antimuscarinic adverse effects are obviously a risk when antimuscarinic antiparkinsonian drugs are given with antipsychotics. Although these are generally mild, serious reactions have occurred. *Trihexyphenidyl*[2] and *orphenadrine*[3] have both been reported to decrease plasma concentrations of chlorpromazine, possibly by interfering

with absorption from the gastrointestinal tract. Reports suggesting that antimuscarinics may antagonise the antipsychotic effects of antipsychotics at the neurotransmitter level require substantiating.

1. Perovich RM, *et al.* The behavioral toxicity of bromocriptine in patients with psychiatric illness. *J Clin Psychopharmacol* 1989; 9: 417–22.
2. Rivera-Calimlim L, *et al.* Effects of mode of management on plasma chlorpromazine in psychiatric patients. *Clin Pharmacol Ther* 1973; 14: 978–86.
3. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; 2: 197–208.

Antipsychotics. Elevated plasma levels of haloperidol were reported[1] in a patient being treated for schizophrenia when *chlorpromazine* or *clozapine* were also given.

1. Allen SA. Effect of chlorpromazine and clozapine on plasma concentrations of haloperidol in a patient with schizophrenia. *J Clin Pharmacol* 2000; 40: 1296–7.

Antivirals. *Ritonavir* may increase the plasma concentration of some antipsychotics. The increases expected for pimozide were considered in licensed product information for ritonavir to be large enough to recommend that these drugs should not be used together. Other classical antipsychotics predicted to have increases include haloperidol, perphenazine, and thioridazine; it was recommended that monitoring of drug concentrations and/or adverse effects were required when used with ritonavir.

Beta blockers. Chlorpromazine and *propranolol* may mutually inhibit each other's hepatic metabolism. Propranolol has been reported to increase plasma concentrations of chlorpromazine[1] and thioridazine,[2,3] and *pindolol* to increase plasma-thioridazine concentrations.[4] Neither beta blocker tested had a significant effect on haloperidol concentrations,[3,4] although there is a report of severe hypotension or cardiopulmonary arrest occurring on 3 occasions in a schizophrenic patient given haloperidol with propranolol.[5] The clinical significance of antipsychotic-beta blocker interactions is unclear.

For the effect of chlorpromazine on propranolol, see Anxiolytics and Antipsychotics, under Interactions of Beta Blockers, p. 1322.1.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. The use of antipsychotics, and pimozide in particular, with *sotalol* should be avoided.

1. Peet M, *et al.* Pharmacokinetic interaction between propranolol and chlorpromazine in schizophrenic patients. *Lancet* 1980; ii: 978.
2. Silver JM, *et al.* Elevation of thioridazine plasma levels by propranolol. *Am J Psychiatry* 1986; 143: 1290–2.
3. Greendyke RM, Kanter DR. Plasma propranolol levels and their effect on plasma thioridazine and haloperidol concentrations. *J Clin Psychopharmacol* 1987; 7: 178–82.
4. Greendyke RM, Gulya A. Effect of pindolol administration on serum levels of thioridazine, haloperidol, phenytoin, and phenobarbital. *J Clin Psychiatry* 1988; 49: 105–7.
5. Alexander HE, *et al.* Hypotension and cardiopulmonary arrest associated with concurrent haloperidol and propranolol therapy. *JAMA* 1984; 252: 87–8.

Buspirone. The use of haloperidol with buspirone has resulted in increased serum haloperidol concentrations. However, while some[1] found the mean rise in serum-haloperidol concentrations to be 26%, that seen by others[2] was not statistically significant.

1. Goff DC, *et al.* An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* 1991; 11: 193–7.
2. Huang HF, *et al.* Lack of pharmacokinetic interaction between buspirone and haloperidol in patients with schizophrenia. *J Clin Pharmacol* 1996; 36: 963–9.

Cimetidine. Despite expectations that cimetidine might reduce the metabolism of chlorpromazine, mean steady-state plasma concentrations of chlorpromazine fell rather than rose in 8 patients given cimetidine for 7 days in addition to regular chlorpromazine therapy.[1] The explanation was probably that cimetidine interfered with chlorpromazine absorption. Excessive sedation, necessitating a reduction in chlorpromazine dosage, has been reported[2] after addition of cimetidine to the drug therapy of 2 chronic schizophrenics.

1. Howes CA, *et al.* Reduced steady-state plasma concentrations of chlorpromazine and indomethacin in patients receiving cimetidine. *Eur J Clin Pharmacol* 1983; 24: 99–102.
2. Byrne A, O'Shea B. Adverse interaction between cimetidine and chlorpromazine in two cases of chronic schizophrenia. *Br J Psychiatry* 1989; 155: 413–15.

Cocaine. The risk of antipsychotic-induced dystonic reactions may be increased in cocaine abusers. Dystonia occurred in 6 of 7 cocaine abusers treated with haloperidol.[1]

1. Kumor K, *et al.* Haloperidol-induced dystonia in cocaine addicts. *Lancet* 1986; ii: 1341–2.

Desferrioxamine. Loss of consciousness lasting 48 to 72 hours occurred in 2 patients given prochlorperazine during desferrioxamine therapy.[1] Prochlorperazine may enhance the removal of transition metals from brain cells by desferrioxamine.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; 56: 345–55.

Disulfiram. A psychotic patient, previously maintained with plasma-perphenazine concentrations of 2 to 3 nanomol/mL on an oral dose of 8 mg twice daily, was readmitted with subtherapeutic plasma-perphenazine concentrations of less than 1 nanomol/mL, despite unchanged dosage, after disulfiram therapy.[1] The concentration of the sulfoxide metabolite of perphenazine was much increased. After a change from oral to intramuscular perphenazine therapy there was a substantial clinical improvement associated with a return to therapeutic plasma concentrations of perphenazine and a fall in concentration of the metabolite. Disulfiram appears to greatly enhance biotransformation of oral perphenazine to inactive metabolites, but parenteral administration avoids the 'first-pass' effect in the liver.

1. Hansen LB, Larsen N-E. Metabolic interaction between perphenazine and disulfiram. *Lancet* 1982; ii: 1472.

General anaesthetics. A schizophrenic patient without a history of epilepsy who was receiving oral chlorpromazine and flupentixol depot injection had a convulsive seizure when given *enflurane* anaesthesia.[1]

1. Vohra SB. Convulsions after enflurane in a schizophrenic patient receiving neuroleptics. *Can J Anaesth* 1994; 41: 420–2.

Naltrexone. Two patients maintained on thioridazine experienced intense sleepiness and lethargy after receiving 2 doses of naltrexone.[1]

1. Maany I, *et al.* Interaction between thioridazine and naltrexone. *Am J Psychiatry* 1987; 144: 966.

NSAIDs. A report of severe drowsiness and confusion in patients given haloperidol with *indometacin*.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; i: 830–1.

Opioid analgesics. For reference to the effects of phenothiazines on *pethidine*, see p. 123.3.

Piperazine. There has been an isolated report[1] of convulsions associated with the use of chlorpromazine in a child who had received piperazine several days earlier. Subsequent *animal*[1-3] studies produced conflicting evidence for an interaction and it was suggested[3] that an interaction would only be clinically significant when high concentrations of piperazine were reached in the body.

1. Boulos BM, Davis LE. Hazard of simultaneous administration of phenothiazine and piperazine. *N Engl J Med* 1969; 280: 1245–6.
2. Armbrecht BH. Reaction between piperazine and chlorpromazine. *N Engl J Med* 1970; 282: 1490–1.
3. Sturman G. Interaction between piperazine and chlorpromazine. *Br J Pharmacol* 1974; 50: 153–5.

Sympathomimetics. For reference to the possible interaction between phenothiazines and *adrenaline*, see Treatment of Adverse Effects, p. 1050.3.

A 27-year-old woman with schizophrenia and T-wave abnormality of the heart,[1] receiving thioridazine 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of also taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with *phenylpropanolamine hydrochloride* 50 mg (*Contac C*).

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; 119: 729–31.

Tobacco smoking. Smoking has been shown to decrease the incidence of chlorpromazine-induced sedation[1,2] and orthostatic hypotension.[2] Studies indicate that the clearance of chlorpromazine,[3] fluphenazine,[4] tiotixene,[5] haloperidol,[6] and thioridazine[7] may be increased in patients who smoke. It has been suggested that some of the components of smoke may act as liver-enzyme inducers. The clinical significance of this effect is unclear but the possible need to use increased doses in smokers should be borne in mind.

1. Swett C. Drowsiness due to chlorpromazine in relation to cigarette smoking: a report from the Boston Collaborative Drug Surveillance Program. *Arch Gen Psychiatry* 1974; 31: 211–13.
2. Pantuck EJ, *et al.* Cigarette smoking and chlorpromazine disposition and actions. *Clin Pharmacol Ther* 1982; 31: 533–8.
3. Chetty M, *et al.* Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol* 1994; 46: 523–6.
4. Ereshefsky L, *et al.* Effects of smoking on fluphenazine clearance in psychiatric inpatients. *Biol Psychiatry* 1985; 20: 329–32.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; 11: 296–301.
6. Jann MW, *et al.* Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology (Berl)* 1986; 90: 468–70.
7. Berecz R, *et al.* Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype. *Eur J Clin Pharmacol* 2003; 59: 45–50.

Vitamins. Giving *ascorbic acid*, for vitamin C deficiency, to a patient receiving fluphenazine for bipolar disorder was associated with a fall in serum concentrations of fluphenazine and a deterioration of behaviour.[1]

1. Dysken MW, *et al.* Drug interaction between ascorbic acid and fluphenazine. *JAMA* 1979; 241: 2008.

Xanthine-containing beverages. Studies *in vitro* have shown precipitation of some antipsychotics from solution by addition of *coffee* and *tea*.[1,2] However, in a study of 16 patients taking antipsychotics no correlation could be found between plasma-antipsychotic concentrations or behaviour and tea or coffee consumption.[3]

1. Kulhanek F, *et al.* Precipitation of antipsychotic drugs in interaction with coffee or tea. *Lancet* 1979; ii: 1130.
2. Lasswell WL, *et al.* In vitro interaction of neuroleptics and tricyclic antidepressants with coffee, tea, and gallotannic acid. *J Pharm Sci* 1984; 73: 1056–8.
3. Bowen S, *et al.* Effect of coffee and tea on blood levels and efficacy of antipsychotic drugs. *Lancet* 1981; i: 1217–18.

Pharmacokinetics

Chlorpromazine is readily, although sometimes erratically, absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after ingestion. It is subject to considerable first-pass metabolism in the gut wall and is also extensively metabolised in the liver and is excreted in the urine and bile in the form of many active and inactive metabolites; there is some evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after intramuscular doses. Moreover, there is very wide intersubject variation in plasma concentrations of chlorpromazine; no simple correlation has been found between plasma concentrations of chlorpromazine and its metabolites, and their therapeutic effect (see Administration under Uses and Administration, p. 1046.1). Paths of metabolism of chlorpromazine include hydroxylation and conjugation with glucuronic acid, *N*-oxidation, oxidation of a sulfur atom, and dealkylation. Although the plasma half-life of chlorpromazine itself has been reported to be about 30 hours, elimination of the metabolites may be very prolonged. There is limited evidence that chlorpromazine induces its own metabolism.

Chlorpromazine is about 95 to 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ampliactil; Conrax; ***Austral.***: Largactil; ***Braz.***: Amplictil; Clopsina; Clorpromaz; Longactil; ***Chile***: Largactil; *Cz.*: Plegomazin; ***Fin.***: Klorpromaz; ***Fr.***: Largactil; ***Gr.***: Largactil; Solidon; Zuledin; ***Hung.***: Hibernal; ***India***: Cain; Clozine; Emetil; Megatil; ***Indon.***: Cepezet; Meprosetil; Promactil; ***Irl.***: Clonactil; Clonazine†; ***Israel***: Taroctyl; ***Ital.***: Largactil; Prozin; ***Jpn***: Wintermin; ***Malaysia***: Matcine; ***Mex.***: Largactil; ***NZ***: Largactil; ***Philipp.***: Globazine; Laractyl; Proma; Promazine; Psynor; Thorazine; ***Pol.***: Fenactil; ***Port.***: Largactil; Largatrex†; ***Rus.***: Aminazin (Аминазин); ***S.Afr.***: Largactil; ***Singapore***: Largo; Matcine; ***Spain***: Largactil; ***Switz.***: Chlorazin; ***Thai.***: Chlopazine; Chlorpromasit†; Chlorpromed; Duncan†; Matcine; Plegomazine; Pogetol; Prozine; ***Turk.***: Largactil; ***UK***: Largactil; ***Ukr.***: Aminazin (Аминазин).

Multi-ingredient Preparations. *Arg.*: 6-Copin†; 6-Copin; ***India***: Chlorectil Plus; Clozine Forte; Clozine Plus; Emetil DS; Emetil Plus; Lacalm; Manocalm Forte; Neocalm Forte; Trinicalm Forte; ***Thai.***: Ama.

Pharmacopoeial Preparations

BP 2014: Chlorpromazine Injection; Chlorpromazine Oral Solution; Chlorpromazine Suppositories; Chlorpromazine Tablets;

USP 36: Chlorpromazine Hydrochloride Injection; Chlorpromazine Hydrochloride Oral Concentrate; Chlorpromazine Hydrochloride Syrup; Chlorpromazine Hydrochloride Tablets; Chlorpromazine Suppositories.

Chlorprothixene *(BAN, USAN, rINN)*

Chlorprothixène; Chlorprothixenum; Clorprotixeno; Kloorprotiksseeni; Klorprotixen; N-714; Ro-4-0403; Хлорпротиксен.

(*Z*)-3-(2-Chlorothioxanthen-9-ylidene)-*NN*-dimethylpropylamine.

$C_{18}H_{18}ClNS$=315.9

CAS — 113-59-7.

ATC — N05AF03.

ATC Vet — QN05AF03.

UNII — 9S7OD60EWP.

Pharmacopoeias. In *Chin.*

The symbol † denotes a preparation no longer actively marketed

Chlorprothixene Hydrochloride

(BANM, rINNM)

Chloroprotyksenu chlorowodorek; Chlorprothixène, Chlorhydrate de; Chlorprothixenhydrochlorid; Chlorprothixenhydrochlorid; Chlorprothixeni Hydrochloridum; Chlorprotikseno hidrochloridas; Clorprotixeno; hidrocloruro de; Hidrocloruro de clorprotixeno; Kloorprotikseenihydrokloriidi; Klórprótixen-hidroklorid; Klorprotixenhydroklorid; Хлорпротиксена Гидрохлорид.

$C_{18}H_{19}Cl_2NS$=352.3

ATC — N05AF03.

ATC Vet — QN05AF03.

UNII — 268KCR965N.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Chlorprothixene Hydrochloride). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.4 to 5.2. Protect from light.

Profile

Chlorprothixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.2). It is used mainly in the treatment of psychoses (p. 1030.2). Chlorprothixene is given as the hydrochloride. Preparations of chlorprothixene prepared with the aid of lactic acid have been stated to contain chlorprothixene lactate. The acetate, citrate, and the mesilate have also been used.

Chlorprothixene is usually given orally as the hydrochloride and doses are expressed in terms of this salt. A usual oral initial dose for the treatment of psychoses is 15 to 50 mg three or four times daily, increased according to response; doses of up to 600 mg or more daily have been given in severe or resistant cases. Chlorprothixene should be used in reduced dosage for elderly or debilitated patients.

Adverse effects. A 59-year-old man receiving chlorprothixene (for the second time) for acute mania developed severe obstructive jaundice within a few days; he was also taking chlorpropamide, digoxin, and diuretics.[1] Chlorprothixene was considered the most likely cause of the jaundice, though chlorpropamide could not be excluded.

1. Ruddock DGS, Hoenig J. Chlorprothixene and obstructive jaundice. *BMJ* 1973; 1: 231.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of chlorprothixene on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Chlorprothixene and its sulfoxide metabolite were concentrated in the breast milk of 2 mothers given chlorprothixene 200 mg daily but it was calculated that the amount ingested by the nursing infant was only 0.1% of the maternal dose per kg body-weight.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Presence of chlorprothixene and its metabolites in breast milk. *Eur J Clin Pharmacol* 1984; 27: 611–13.

Metabolism. Results from studies on the metabolism of chlorprothixene in *animals* and man[1] indicated that in addition to the major metabolite chlorprothixene-sulfoxide, 2 further urinary metabolites were identified, namely *N*-desmethylchlorprothixene-sulfoxide and chlorprothixene-sulfoxide-*N*-oxide.

1. Raaflaub J. Zum Metabolismus des Chlorprothixen. *Arzneimittelforschung* 1967; 17: 1393–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorprothixene as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Truxal; *Denm.*: Truxal; *Fin.*: Truxal; *Ger.*: Truxal; *Gr.*: Truxal; *Hung.*: Truxal; *Neth.*: Truxal; *Norw.*: Truxal; *Rus.*: Truxal (Труксал); *Swed.*: Truxal; *Switz.*: Truxal; Truxaletten†; *Ukr.*: Truxal (Труксал).

Cinolazepam *(rINN)*

Cinolazépam; Cinolazepamum; OX-373; Цинолазепам.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-3-hydroxy-2-oxo-1*H*-1,4-benzodiazepine-1-propionitrile.

$C_{18}H_{13}ClFN_3O_2$=357.8

CAS — 75696-02-5.

ATC — N05CD13.

ATC Vet — QN05CD13.

UNII — 68P0556B0U.

Profile

Cinolazepam is a benzodiazepine derivative with general properties similar to those of diazepam (p. 1063.2) that has been used in the short-term management of sleep disorders in usual oral doses of 40 mg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Gerodorm; *Cz.*: Gerodorm; *Hung.*: Gerodorm.

Clocapramine Hydrochloride *(rINNM)*

Chlorcarpipramine Hydrochloride; Clocapramina, hidrocloruro de; Clocapramine, Chlorhydrate de; Clocapramini Hydrochloridum; Hidrocloruro de clocapramina; Y-4153; Клокапрамина Гидрохлорид.

1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl][1,4′-bipiperidine]-4′-carboxamide dihydrochloride monohydrate.

$C_{28}H_{37}ClN_4O,2HCl,H_2O$=572.0

CAS — 47739-98-0 (clocapramine); 28058-62-0 (clocapramine hydrochloride).

UNII — 9NLU6H3LRD.

Pharmacopoeias. In *Jpn.*

Profile

Clocapramine is a chlorinated derivative of carpipramine (p. 1044.2). The hydrochloride is given orally in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Clofekton; Padrasen.

Clomethiazole *(BAN, rINN)*

Chlormethiazole; Clométhiazole; Clomethiazolum; Clometiazol; Klometiatsoli; Klometiazol; Клометиазол.

5-(2-Chloroethyl)-4-methyl-1,3-thiazole.

C_6H_8ClNS=161.6

CAS — 533-45-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

UNII — 0C5DBZ19HV.

Pharmacopoeias. In *Br.*

BP 2014: (Clomethiazole). A colourless to slightly yellowish-brown liquid with a characteristic odour. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. A 0.5% solution in water has a pH of 5.5 to 7.0. Store at a temperature of 2 degrees to 8 degrees.

Clomethiazole Edisilate *(BANM, rINNM)*

Chlormethiazole Edisylate; Chlormethiazole Ethanedisulphonate; Clométhiazole, Edisilate de; Clomethiazole Edisylate (USAN); Clomethiazoli Edisilas; Clometiazol, edisilato de; Edisilato de clometiazol; Klometiazolu edysylan; NEX-002; Клометиазола Эдизилат.

5-(2-Chloroethyl)-4-methylthiazole ethane-1,2-disulphonate.

$(C_6H_8ClNS)_2C_2H_6O_6S_2$=513.5

CAS — 1867-58-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

UNII — 22NJI0W1D2.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Clomethiazole Edisilate). A white crystalline powder with a characteristic odour. Freely soluble in water; soluble in alcohol; practically insoluble in ether.

Incompatibility. Several studies have shown that clomethiazole edisilate may permeate through or be sorbed onto plastics used in intravenous infusion bags or giving sets.[1-4] The drug may also react with and soften the plastic.[1] Licensed product information has suggested that thrombophlebitis, fever, and headache reported in young children during prolonged infusions may have been due to reaction with plastic giving sets and silastic cannulae. Recommendations for intravenous use have therefore included the use of a motor-driven glass syringe in preference to a plastic drip set in small children, changing plastic drip sets at least every 24 hours when used in older patients, and use of teflon intravenous cannulas.

1. Lingam S, *et al.* Problems with intravenous chlormethiazole (Heminevrin) in status epilepticus. *BMJ* 1980; 280: 155–6.
2. Tsuei SE, *et al.* Sorption of chlormethiazole by intravenous infusion giving sets. *Eur J Clin Pharmacol* 1980; 18: 333–8.
3. Kowaluk EA, *et al.* Dynamics of clomethiazole edisylate interaction with plastic infusion systems. *J Pharm Sci* 1984; 73: 43–7.
4. Lee MG. Sorption of four drugs to polyvinyl chloride and polybutadiene intravenous administration sets. *Am J Hosp Pharm* 1986; 43: 1945–50.

Uses and Administration

Clomethiazole is a hypnotic and sedative with anticonvulsant effects. It is used orally in the treatment of agitation and restlessness (see Disturbed Behaviour, p. 1030.2) in elderly patients, in the short-term management of severe insomnia (p. 1033.2) in the elderly, and in the treatment of acute alcohol withdrawal symptoms (p. 1735.1). It was also given as an intravenous infusion in the management of status epilepticus and impending or actual eclampsia; however, a parenteral formulation of clomethiazole no longer appears to be available.

In the UK, clomethiazole is available as capsules containing 192 mg of clomethiazole base and as syrup containing 250 mg of the edisilate in 5 mL. As a result of differences in the bioavailability of these preparations, 192 mg of the base in the capsules is considered therapeutically equivalent to 250 mg (5 mL) of the edisilate in the syrup, i.e. one capsule or 5 mL of syrup are equivalent in their effects.

The usual hypnotic dose of clomethiazole for **insomnia** is 1 or 2 capsules (192 or 384 mg of the base) or the equivalent before bedtime. For **restlessness and agitation** 1 capsule (192 mg of the base), or the equivalent, may be given 3 times daily.

Various clomethiazole regimens have been suggested for the treatment of **alcohol withdrawal**, usually starting with 2 to 4 capsules, or the equivalent, which may be repeated after some hours if necessary. In the first 24 hours, 9 to 12 capsules, or the equivalent, divided into 3 or 4 doses, can be given; the dose is then gradually reduced over the next 5 days. Treatment should be carried out in hospital or in specialist centres, and use for longer than 9 days is not recommended because of the risk of dependence (see below).

Porphyria. Clomethiazole is one of the drugs that has been used for seizure prophylaxis in patients with porphyria who continue to have convulsions while in remission. However, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clomethiazole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Stroke. Clomethiazole has been studied[1,2] as a neuroprotective drug in the acute management of patients with stroke, but no beneficial effect on long-term outcome was found.

1. Wahlgren NG, *et al.* CLASS Study Group. Clomethiazole Acute Stroke Study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. *Stroke* 1999; 30: 21–8.
2. Lyden P, *et al.* Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. *Stroke* 2002; 33: 122–8.

Substance dependence. For a discussion of the management of *opioid* withdrawal symptoms, including mention of the use of clomethiazole, see p. 109.2.

Dependence and Withdrawal

Dependence may develop, particularly with prolonged use of higher than recommended doses of clomethiazole. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects, Treatment, and Precautions

Clomethiazole may produce nasal congestion and irritation, sneezing, and conjunctival irritation sometimes associated with a headache. Nasopharyngeal or bronchial secretions may be increased. Skin rashes and urticaria have also occurred and in rare cases bullous eruptions have been reported. Gastrointestinal disturbances including nausea and vomiting have been reported after oral doses. Reversible increases in liver enzyme values and blood-bilirubin concentrations have also been noted. Clomethiazole can cause excessive drowsiness, particularly in high

doses; drowsiness may persist the next day, and patients affected should not drive or operate machinery. Paradoxical excitation or confusion may occur rarely. Anaphylaxis has also been reported rarely.

Excessive doses may produce coma, respiratory depression, hypotension, and hypothermia; pneumonia may follow increased respiratory secretion. Treatment is as for barbiturate overdose (see Amobarbital, p. 1038.1).

Clomethiazole is contra-indicated in patients with acute pulmonary insufficiency, and should be given with care to patients with sleep apnoea syndrome, chronic pulmonary insufficiency, or renal, liver, cerebral, or cardiac disease. Clomethiazole should be given with caution to elderly patients as there may be increased bioavailability and delayed elimination. Paradoxical worsening of epilepsy may occur in the Lennox Gastaut syndrome.

Administration by intravenous infusion. Severe adverse effects have followed the intravenous use of clomethiazole, and intravenous preparations are no longer generally available. Facilities for intubation and resuscitation were required when clomethiazole was given intravenously, with care taken to ensure that the patient's airway was maintained since there is a risk of mechanical obstruction during deep sedation. At too high a rate of infusion, sleep induced with clomethiazole could lapse into deep unconsciousness and patients required close and constant observation. Rapid infusion has also caused transient apnoea and hypotension, and special care was needed in patients susceptible to cerebral or cardiac complications, including the elderly. With prolonged infusion there was also a risk of electrolyte imbalance due to the water load involved with the glucose vehicle. Recovery has been considerably delayed after prolonged infusion.

Effects on the heart. Cardiac arrest in 2 chronic alcoholics might have been associated with clomethiazole infusion.[1]

1. McInnes GT, *et al.* Cardiac arrest following chlormethiazole infusion in chronic alcoholics. *Postgrad Med J* 1980; 56: 742–3.

Overdosage. A report of clomethiazole poisoning on 16 occasions in 13 patients, some of whom had also taken other drugs and alcohol.[1] There was increased salivation on 7 occasions; otherwise the clinical features were those of barbiturate poisoning (see Adverse Effects of Amobarbital, p. 1038.1). The highest plasma-clomethiazole concentration was 36 micrograms/mL, with the highest value in a conscious patient 11.5 micrograms/mL. All the patients survived following intensive supportive treatment as for barbiturate poisoning.

1. Illingworth RN, *et al.* Severe poisoning with chlormethiazole. *BMJ* 1979; 2: 902–3.

Parotitis. Acute bilateral parotitis has been reported in a patient given clomethiazole.[1] The swelling disappeared after withdrawal of clomethiazole and recurred on rechallenge.

1. Bosch X, *et al.* Parotitis induced by chlormethiazole. *BMJ* 1994; 309: 1620.

Pregnancy. There have been reports of neonates being adversely affected by clomethiazole given to their mothers for pre-eclampsia or eclampsia;[1,2] effects included sedation, hypotonia, and apnoea. It was suggested that the effects might have been due to a synergistic interaction between clomethiazole and diazoxide as these drugs were given to most of the mothers with affected infants.[1]

1. Johnson RA. Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide. *BMJ* 1976; 1: 943.
2. Wood C, Renou P. Sleepy and hypotonic neonates. *Med J Aust* 1978; 2: 73.

Interactions

The sedative effects of clomethiazole are enhanced by CNS depressants such as alcohol, barbiturates, other hypnotics and sedatives, and antipsychotics.

Alcohol. Although clomethiazole has been a popular choice for the treatment of alcohol withdrawal symptoms (p. 1735.1), if it is given long-term, patients readily transfer dependency to it; if they also continue to abuse alcohol this may lead to severe self-poisoning with deep coma and potentially fatal respiratory depression.[1]

1. McInnes GT. Chlormethiazole and alcohol: a lethal cocktail. *BMJ* 1987; 294: 592.

Beta blockers. Sinus bradycardia developed in an 84-year-old woman taking *propranolol* for hypertension 3 hours after she took a second dose of clomethiazole 192 mg.[1] Her pulse rate increased on stopping propranolol and clomethiazole and later stabilised when she took propranolol with haloperidol.

1. Adverse Drug Reactions Advisory Committee (Australia). *Med J Aust* 1979; 2: 553.

Diazoxide. For a report of adverse reactions in neonates born to mothers given clomethiazole and diazoxide, see Pregnancy under Adverse Effects, Treatment, and Precautions, above.

Histamine H_2-antagonists. Use of *cimetidine* 1 g daily for 1 week increased sleep time induced by a 1-g oral dose of clomethiazole edisilate in most of 8 healthy subjects from between 30 to 60 minutes to at least 2 hours.[1] This was associated with a 31% reduction in the mean clearance of clomethiazole, a 69% rise in the mean peak plasma concentration of the hypnotic, and an increase in its mean elimination half-life from 2.33 to 3.63 hours.

Ranitidine did not significantly affect the pharmacokinetics of clomethiazole in a study in 7 healthy subjects.[2]

1. Shaw G, *et al.* Cimetidine impairs the elimination of chlormethiazole. *Eur J Clin Pharmacol* 1981; 21: 83–5.
2. Mashford ML, *et al.* Ranitidine does not affect chlormethiazole or indocyanine green disposition. *Clin Pharmacol Ther* 1983; 34: 231–3.

Pharmacokinetics

Clomethiazole is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 15 to 90 minutes after oral doses depending on the formulation used. It is widely distributed in the body and is reported to be 65% bound to plasma proteins. Clomethiazole is extensively metabolised, probably by first-pass metabolism in the liver with only small amounts appearing unchanged in the urine. The elimination half-life has been reported to be about 4 hours but this may be increased to 8 hours or longer in the elderly or in patients with hepatic impairment. Clomethiazole crosses the placenta and is distributed into breast milk.

Hepatic impairment. Studies in 8 patients with advanced cirrhosis of the liver and in 6 healthy men showed that the amount of unmetabolised clomethiazole reaching the circulation after an oral dose was about 10 times higher in the patients than in the controls.[1] Low concentrations in the controls were related to extensive first-pass metabolism in the liver.

1. Pentikäinen PJ, *et al.* Pharmacokinetics of chlormethiazole in healthy volunteers and patients with cirrhosis of the liver. *Eur J Clin Pharmacol* 1980; 17: 275–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Hemineurin†; *Cz.*: Heminevrin; *Ger.*: Distraneurin; *Gr.*: Distraneurin; Distraneurine; Heminevrin; *Hung.*: Heminevrin; *Irl.*: Heminevrin†; *Norw.*: Heminevrin; *Pol.*: Heminevrin; *Spain*: Distraneurine; *Swed.*: Heminevrin; *Switz.*: Distraneurin; *UK*: Heminevrin†.

Pharmacopoeial Preparations

BP 2014: Clomethiazole Capsules; Clomethiazole Infusion; Clomethiazole Oral Solution.

Cloral Betaine *(BAN, rINN)*

Chloral Betaine (USAN); Cloral betaína; Cloral Bétaïne; Cloralum Betainum; Compound 5107; Хлораль Бетаин.

An adduct of cloral hydrate and betaine.

$C_7H_{12}Cl_3NO_3H_2O$=282.5

CAS — 2218-68-0.

UNII — 8680278NRH.

Profile

Cloral betaine rapidly dissociates in the stomach to release cloral hydrate and has actions and uses similar to those of cloral hydrate (below). It is given orally in the short-term management of insomnia (p. 1033.2), as tablets containing 707 mg (equivalent to about 414 mg of cloral hydrate). The usual hypnotic dose is one or two tablets taken at night with water or milk. The maximum daily dose is five tablets (equivalent to about 2 g of cloral hydrate). A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Somnwell†; Welldorm.

Cloral Hydrate

Chloral Hydrate (BAN); Chloral, hydrate de; Chloralhydrat; Chloralhydrát; Chlorali Hydras; Chloralio hidratas; Chloralu wodzian; Cloral, hidrato de; Kloraalihydraatti; Kloral Hidrat; Kloral-hidrat; Kloralhydrat; Хлоралгидрат.

2,2,2-Trichloroethane-1,1-diol.

$C_2H_3Cl_3O_2$=165.4

CAS — 302-17-0.

ATC — N05CC01.

ATC Vet — QN05CC01.

UNII — 418M5916WG.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of cloral hydrate:

Jellies; Jelly beans; Joy Juice; Knockout Drops; Knock out drops; Mickey; Mickeys; Mickey Finn; Mickey Finns; Peter; Torpedo.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cloral Hydrate). Colourless, transparent crystals. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Cloral Hydrate). Colourless, transparent, or white crystals having an aromatic, penetrating, and slightly acrid odour. It volatilises slowly on exposure to air and melts at about 55 degrees. Soluble 1 in 0.25 of water, 1 in 1.3 of alcohol, 1 in 2 of chloroform, and 1 in 1.5 of ether; very soluble in olive oil. Store in airtight containers.

Incompatibility. Cloral hydrate is reported to be incompatible with alkalis, alkaline earths, alkali carbonates, soluble barbiturates, borax, tannin, iodides, oxidising agents, permanganates, and alcohol (cloral alcoholate may crystallise out). It forms a liquid mixture when triturated with many organic compounds, such as camphor, menthol, phenazone, phenol, thymol, and quinine salts.

Uses and Administration

Cloral hydrate is a hypnotic and sedative with properties similar to those of the barbiturates. It is used in the short-term management of insomnia (p. 1033.2) and has been used for sedation and as a premedicant (see Anaesthesia, p. 1899.1); its use as a hypnotic, particularly in children, is now limited. It has also been used in the management of acute alcohol withdrawal symptoms (p. 1735.1).

Externally, cloral hydrate has a rubefacient action and has been used as a counter-irritant.

Cloral hydrate is given orally as a liquid or dissolved in a suitable vehicle within gelatin capsules. It has also been dissolved in a bland fixed oil and given by enema or as suppositories.

It should not be given as tablets because of the risk of damage to the mucous membrane of the alimentary tract.

The usual oral hypnotic dose is 0.5 to 1 g given as a single dose at night; as a sedative 250 mg can be given three times daily. The maximum daily dose for both indications is 2 g. Oral dosage forms should be taken well diluted or with plenty of water or milk.

A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment. For doses in children, see below.

Derivatives of cloral hydrate, such as acetylglycinamide-cloral hydrate, cloral betaine (above), chloralose (p. 2150.2), chloralodol, and dichloralphenazone (p. 1071.3), which break down in the body to yield cloral hydrate, have been used similarly.

Administration in children. Cloral hydrate has been used in the short-term management of insomnia and for sedation and as a premedicant in children; however, carcinogenicity was once a cause for concern (see Carcinogenicity p. 1056.1) and such use is now limited.

Children aged 2 to 11 years may be given cloral hydrate 30 to 50 mg/kg (maximum single dose of 1 g) orally at night as a hypnotic; those aged 12 years and older may be given the usual adult dose for this indication (see Uses and Administration, above).

Although not licensed in the UK for sedation of children before a painless procedure, the *BNFC* suggests the following oral doses, given 45 to 60 minutes beforehand: neonates and children up to 12 years of age, 30 to 50 mg/kg, although up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring; 12 to 18 years, 1 to 2 g. Doses may be given rectally if the oral route cannot be used.

Dependence and Withdrawal, Adverse Effects, and Treatment

Cloral hydrate has an unpleasant taste and is corrosive to skin and mucous membranes unless well diluted. The most frequent adverse effect is gastric irritation; abdominal distension and flatulence may also occur. CNS effects such as drowsiness, light-headedness, ataxia, headache, paradoxical excitement, hallucinations, nightmares, delirium, and confusion (sometimes with paranoia) occur occasionally. Hypersensitivity reactions include rashes (erythema multiforme and Stevens-Johnson syndrome have been reported with the related compound triclofos). Ketonuria may occur.

The effects of acute overdosage resemble acute barbiturate intoxication (see Amobarbital, p. 1038.1 and

Overdosage below), and are managed similarly. In addition the irritant effect may cause initial vomiting, and gastric necrosis leading to strictures. Cardiac arrhythmias have been reported. Jaundice may follow liver damage, and albuminuria may follow kidney damage.

Tolerance may develop and dependence may occur. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p. 1038.1).

Incidence of adverse effects. In a drug surveillance programme,[1] adverse effects of cloral hydrate, which were reversible, occurred in 2.3% of 1130 patients evaluated and included gastrointestinal symptoms (10 patients), CNS depression (20), and rash (5). In 1 patient the prothrombin time was increased; in another hepatic encephalopathy seemed to worsen; and bradycardia developed in a further patient. In another such programme, adverse effects occurred in about 2% of 5435 patients given cloral hydrate.[2] Three reactions were described as life-threatening.

1. Shapiro S, *et al.* Clinical effects of hypnotics II: an epidemiologic study. *JAMA* 1969; **209**: 2016–20.
2. Miller RR, Greenblatt DJ. Clinical effects of chloral hydrate in hospitalized medical patients. *J Clin Pharmacol* 1979; **19**: 669–74.

Carcinogenicity. Cloral hydrate has been widely used as a sedative, especially in children. Concern over warnings that cloral hydrate was carcinogenic in *rodents*[1] has prompted some experts, including the American Academy of Pediatrics, to review the relative risks of the medical use of this drug.[2,3] The original warnings appear to have been based, in part, on the assumption that cloral hydrate was a reactive metabolite of trichloroethylene and was responsible for its carcinogenicity, but there is evidence to suggest that the carcinogenicity of trichloroethylene is due to a reactive intermediate epoxide metabolite. Studies *in vitro* indicate that cloral hydrate can damage chromosomes in some mammalian test systems but there have been no studies of the carcinogenicity of cloral hydrate in humans. Some long-term studies in *mice* have linked cloral hydrate with the development of hepatic adenomas or carcinomas. However, it was noted that cloral hydrate was not the only sedative that had been shown to be a carcinogen in experimental *animals*. The American Academy of Pediatrics considered cloral hydrate to be an effective sedative with a low incidence of acute toxicity when given short-term as recommended and, although the information on carcinogenicity was of concern, it was not sufficient to justify the risk associated with the use of less familiar sedatives. There was no evidence in infants or children showing that any of the available alternatives were safer or more effective. However, the use of repetitive dosing with cloral hydrate to maintain prolonged sedation in neonates and other children was of concern because of the potential for accumulation of drug metabolites and resultant toxicity.

A more recent cohort study[4] found no persuasive evidence to support a relationship between the use of cloral hydrate and the development of cancer. However, the statistical power was low for weak associations, particularly for some individual cancer sites.

1. Smith MT. Chloral hydrate warning. *Science* 1990; **250**: 359.
2. Steinberg AD. Should chloral hydrate be banned? *Pediatrics* 1993; **92**: 442–6.
3. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. *Pediatrics* 1993; **92**: 471–3.
4. Haselkorn T, *et al.* Short-term chloral hydrate administration and cancer in humans. *Drug Safety* 2006; **29**: 67–77.

Effects on the CNS. A 2-year-old child[1] had the first of 2 seizures 60 minutes after receiving cloral hydrate 70 mg/kg for sedation.

1. Muñoz M, *et al.* Seizures caused by chloral hydrate sedative doses. *J Pediatr* 1997; **131**: 787–8.

Hyperbilirubinaemia. Small retrospective studies[1] have suggested that prolonged use of cloral hydrate in neonates may be associated with the development of hyperbilirubinaemia. This may possibly be related to the prolonged half-life of the metabolite trichloroethanol in neonates.

1. Lambert GH, *et al.* Direct hyperbilirubinemia associated with chloral hydrate administration in the newborn. *Pediatrics* 1990; **86**: 277–81.

Overdosage. The general management of poisoning with cloral hydrate resembles that for barbiturates (see Treatment of Adverse Effects, under Amobarbital, p. 1038.1). Activated charcoal may be given orally to drug-naive adults and children within 1 hour of ingestion of more than 50 mg/kg, provided that the airway can be protected; for those already receiving cloral hydrate, consider giving activated charcoal if double the therapeutic dose has been taken. However, the value of gastric decontamination for overdose is uncertain. Of 76 cases of cloral hydrate poisoning reported to the UK National Poisons Information Service (NPIS), 47 were severe.[1] Of 39 adults, 12 had cardiac arrhythmias including 5 with cardiac arrest. Antiarrhythmic drugs were recommended unless obviously contra-indicated. Haemoperfusion through charcoal or haemodialysis was recommended for patients in prolonged coma. Cardiac arrhythmias and CNS depression were also major features of 12 cases of cloral hydrate overdosage reported from Australia.[2] Lidocaine was not always successful in controlling arrhythmias, but propranolol was successful in all 7 patients in whom it was used. It was noted that resistant arrhythmias, particularly ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, were the usual cause of death in patients who had taken an overdosage of cloral hydrate. Although there had been no controlled studies of antiarrhythmic therapy in overdosage with cloral hydrate, the successful use of beta blockers appeared to be a recurring feature in reports in the literature. Indeed, the UK NPIS notes that tachyarrhythmias usually respond readily to an intravenous beta blocker such as esmolol or metoprolol.

Giving flumazenil produced an increased level of consciousness, pupillary dilatation, and return of respiratory rate and blood pressure towards normal in a patient who had taken an overdosage of cloral hydrate.[3]

1. Wiseman HM, Hampel G. Cardiac arrhythmias due to chloral hydrate poisoning. *BMJ* 1978; **2**: 960.
2. Graham SR, *et al.* Overdose with chloral hydrate: a pharmacological and therapeutic review. *Med J Aust* 1988; **149**: 686–8.
3. Donovan KL, Fisher DJ. Reversal of chloral hydrate overdose with flumazenil. *BMJ* 1989; **298**: 1253.

Precautions

Cloral hydrate should not be used in patients with marked hepatic or renal impairment or severe cardiac disease, and oral dosage is best avoided in the presence of gastritis. As with all sedatives, it should be used with caution in those with respiratory insufficiency.

Cloral hydrate can cause drowsiness that may persist the next day; affected patients should not drive or operate machinery. Prolonged use and abrupt withdrawal of cloral hydrate should be avoided to prevent precipitation of withdrawal symptoms. Repeated doses in infants and children may lead to accumulation of metabolites and thereby increase the risk of adverse effects. Use is best avoided during pregnancy.

Cloral hydrate may interfere with some tests for urinary glucose or 17-hydroxycorticosteroids.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, use of cloral hydrate by breast-feeding mothers has been reported to cause sleepiness in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Neonates. The half-life of trichloroethanol, an active metabolite of cloral hydrate, is prolonged in neonates;[1] values of up to 66 hours have been reported in some studies. Short-term sedation in the neonate with single oral doses of 25 to 50 mg/kg of cloral hydrate is considered[1] to be probably relatively safe, but repeated dosage carries the risk of accumulation of metabolites which may result in serious toxicity. Toxic reactions may occur even after the drug has been stopped since the metabolites may accumulate for several days.

1. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31**: 423–43.

Obstructive sleep apnoea. Children with obstructive sleep apnoea could be at risk from life-threatening respiratory obstruction if cloral hydrate is used for sedation. Details of 2 such children who suffered respiratory failure after sedation with cloral hydrate for lung function studies have been reported.[1]

1. Biban P, *et al.* Adverse effect of chloral hydrate in two young children with obstructive sleep apnea. *Pediatrics* 1993; **92**: 461–3.

Porphyria. Although cloral hydrate has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] UK licensed product information recommends that it should not be used in patients susceptible to acute attacks of porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The sedative effects of cloral hydrate are enhanced by other CNS depressants such as alcohol (the 'Mickey Finn' of detective fiction), barbiturates, and other sedatives.

Cloral hydrate may alter the effects of coumarin anticoagulants (see Warfarin, p. 1533.1). A hypermetabolic state, apparently due to displacement of thyroid hormones from their binding proteins, has been reported in patients given an intravenous dose of furosemide subsequent to cloral hydrate.

Pharmacokinetics

Cloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral doses. It is widely distributed throughout the body. It is rapidly metabolised to trichloroethanol and trichloroacetic acid (p. 1727.2) in the erythrocytes, liver, and other tissues. It is excreted partly in the urine as trichloroethanol and its glucuronide (urochloralic acid) and as trichloroacetic acid. Some is also excreted in the bile.

Trichloroethanol is the active metabolite, and passes into the CSF, into breast milk, and across the placenta. The half-life of trichloroethanol in plasma is reported to range from about 7 to 11 hours but is considerably prolonged in the neonate. Trichloroacetic acid has a plasma half-life of several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Kloral; *Ger.*: Chloraldurat†; *Singapore*: Little's Chloral Syrup Paed; *Switz.*: Chloraldurat†; Nervifene; *UK*: Welldorm; *USA*: Aquachloral†; Somnote†.

Multi-ingredient Preparations. *Belg.*: Dentophar†; Sedemol; Sulfa-Sedemol; *Rus.*: Efcamon (Эфкамон); *Turk.*: Dilan†.

Pharmacopoeial Preparations
BP 2014: Cloral Hydrate Oral Solution;
USP 36: Cloral Hydrate Capsules; Cloral Hydrate Syrup.

Clorazepic Acid *(BAN)*

Clorazépico, ácido.
7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid.
$C_{16}H_{11}ClN_2O_3$=314.7
CAS — 23887-31-2; 20432-69-3.
UNII — D51WO0G0L4.

Clorazepate Monopotassium *(USAN)*

Abbott-39083; 4311-CB; Clorazepato monopotásico; Моно-калий Клоразепата.
Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate.
$C_{16}H_{10}ClKN_2O_3$=352.8
CAS — 5991-71-9.
UNII — MS63G8NQUI.

Dipotassium Clorazepate *(BANM, rINN)*

Abbott-35616; AH-3232; 4306-CB; Clorazépate Dipotassique; Clorazepate Dipotassium (USAN); Clorazepato de dipotasio; Dikalii Clorazepas; Dikalio klorazepatas; Dikaliumclorazepat; Dikaliumkloratsepaatti; Dikaliumklorazepat; Dikálium-klórazepát; Kalii Clorazepas; Kaliumkloratsepaatti; Klaiumklorazepat; Klorazepát didraselná sůl; Klorazepat Dipotasyum; Potassium Clorazepate; Дикалия Клоразепат.
Compound of Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate with potassium hydroxide.
$C_{16}H_{11}ClK_2N_2O_4$=408.9
CAS — 57109-90-7.
ATC — N05BA05.
ATC Vet — QN05BA05.
UNII — 63FN7G03XY.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dipotassium Clorazepate). A white or light yellow, crystalline powder. Solutions in water and in alcohol are unstable and should be used immediately. Freely soluble or very soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Clorazepate Dipotassium). A light yellow, crystalline powder which darkens on exposure to light. Soluble in water but, upon standing, may precipitate from the solution; slightly soluble in alcohol and in isopropyl alcohol; practically insoluble in acetone, in chloroform, in dichloromethane, in ether, and in benzene. Store under nitrogen in airtight containers. Protect from light.

Uses and Administration

Clorazepate is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is mainly used in the short-term treatment of anxiety disorders (p. 1028.1), as an adjunct in the management of epilepsy (p. 506.1), and in the alcohol withdrawal syndrome (p. 1735.1).

Dipotassium clorazepate is usually given orally but preparations for intravenous or intramuscular use are also available in some countries. Modified-release preparations given once daily are available in some countries for maintenance therapy.

For the treatment of **anxiety** a usual oral dose of 30 mg of dipotassium clorazepate daily is given in divided doses, adjusted according to response to within the range of 15 to 60 mg daily. It may also be given as a single dose at night, initially in a dose of 15 mg.

Up to 90 mg has been given daily in divided doses in the management of **epilepsy** or the **alcohol withdrawal syndrome**.

Reduced doses should be given to elderly or debilitated patients; initial doses of 7.5 to 15 mg daily have been suggested for the treatment of anxiety.

For details of doses in children, see below.

Administration in children. As an adjunct in the management of epilepsy, children aged between 9 and 12 years may be given dipotassium clorazepate orally in a maximum initial dose of 7.5 mg twice daily, increased by no more than 7.5 mg every week to a maximum of 60 mg daily; older children may be given the usual adult dose (see p. 1056.3).

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Effects on the liver. Jaundice and hepatic necrosis has been associated with clorazepate.[1]

1. Parker JLW. Potassium clorazepate (Tranxene)-induced jaundice. *Postgrad Med J* 1979; 55: 908–910.

Effects on the nervous system. For reference to extrapyramidal disorders associated with the use of benzodiazepines, including clorazepate, see Diazepam, p. 1066.1.

Hypersensitivity. Pruritus and erythematous rash developed in a patient after taking oral dipotassium clorazepate;[1] although intradermal and patch testing gave negative results, symptoms recurred on rechallenge. Cross-sensitivity to diazepam was seen but not to bentazepam.

1. Azmar RC, *et al.* Hypersensitivity to chlorazepate dipotassium. *Allergy* 2005; 60: 264–5.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Clorazepate is decarboxylated rapidly at the low pH in the stomach to form desmethyldiazepam (nordazepam, p. 1089.3), which is quickly absorbed.

References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; 24: 446–51.
2. Bertler Å, *et al.* Intramuscular bioavailability of chlorazepate as compared to diazepam. *Eur J Clin Pharmacol* 1985; 28: 229–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Justum; Tencilan; Tranxilium; ***Austria***: Tranxilium; ***Belg.***: Tranxene; Uni-Tranxene; ***Braz.***: Tranxilene; ***Canad.***: Novo-Clopate; ***Chile***: Calner; Tranxilium; ***Fr.***: Tranxene; ***Ger.***: Tranxilium; ***Gr.***: Tranxene; ***Hong Kong***: Tranxene; ***Israel***: Tranxal; ***Ital.***: Transene; ***Mex.***: Tranxene; ***Neth.***: Tranxene; Tranxilium†; ***Philipp.***: Tranxene; ***Pol.***: Cloranxen; Tranxene; ***Port.***: Medipax; Tranxene; ***S.Afr.***: Tranxene; ***Singapore***: Tranxene; ***Spain***: Tranxilium; ***Switz.***: Tranxilium; ***Thai.***: Anxene; Anxielax†; Cexene; Cloramed†; Cloraxene†; Cloraze; Clozepate; Deda; Dipot; Dopam; Flulium; Frexene; Gaxene; Manotran†; Polizep; Pomadom†; Posenet†; Sanor; Serene; T-Five; Tenmed; Tranadon-S; Trancap; Tranclor†; Trancon; Tranmed; Tranpate†; Tranpon; Transpon; Tranxene; Tranzep; Uptran; Upzene; Zetran†; ***Turk.***: Anksen; Tranxilene; ***USA***: Tranxene; ***Venez.***: Tranxen.

Multi-ingredient Preparations. ***Arg.***: Eucliton Complex; Maxitratobes†; Tranxilium Digest; Vegestabil; ***Fr.***: Noctran†; ***Spain***: Dorken†.

Pharmacopoeial Preparations

USP 36: Clorazepate Dipotassium Tablets.

Clotiapine *(BAN, rINN)*

Clothiapine (USAN); Clotiapina; Clotiapinum; HF-2159; Клотиапин.

2-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine.

$C_{18}H_{18}ClN_3S$=343.9

CAS — 2058-52-8.

ATC — N05AH06.

ATC Vet — QN05AH06.

UNII — Z05HCY0X1T.

Profile

Clotiapine is a dibenzothiazepine antipsychotic with general properties similar to those of the phenothiazines (see Chlorpromazine, p. 1045.2). It is used in a variety of psychiatric disorders including schizophrenia (p. 1031.3), mania (see Bipolar Disorder, p. 397.2), and anxiety (p. 1028.1). It is given orally in doses ranging from 10 to 200 mg daily in divided doses; up to 360 mg daily has been given in severe or resistant psychoses. It may also be given by slow intravenous or deep intramuscular injection.

Psychoses. A systematic review[1] found that good evidence to support the use of clotiapine over other treatments in acute psychotic illness was lacking.

1. Berk M, *et al.* Clotiapine for acute psychotic illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Etumina; ***Belg.***: Etumine; ***Israel***: Entumin; ***Ital.***: Entumin; ***S.Afr.***: Etomine; ***Spain***: Etumina; ***Switz.***: Entumine.

Clotiazepam *(rINN)*

Clotiazépam; Clotiazepamum; Y-6047; Клотиазепам.

5-(2-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one.

$C_{16}H_{15}ClN_2OS$=318.8

CAS — 33671-46-4.

ATC — N05BA21.

ATC Vet — QN05BA21.

UNII — ZCN055599V.

Pharmacopoeias. In *Jpn*.

Profile

Clotiazepam is a short-acting thienodiazepine with general properties similar to those of diazepam (p. 1063.2). A usual oral dose for the short-term management of anxiety disorders (p. 1028.1) is 5 to 15 mg daily given in divided doses but up to 60 mg daily has been used. For insomnia (p. 1033.2) 10 mg has been given as a single dose at night. An oral dose of 10 to 15 mg has been given for premedication (see Anaesthesia, p. 1899.1). Reduced doses may be required in elderly or debilitated patients.

Effects on the liver. Development of hepatitis in a 65-year-old woman was attributed to clotiazepam begun 7 months earlier.[1] The patient took triazolam and lorazepam without any apparent effect on the liver, and it was speculated that the hepatotoxic effect of clotiazepam was related to the thiophene ring present in the chemical structure.

1. Habersetzer F, *et al.* Clotiazepam-induced acute hepatitis. *J Hepatol* 1989; 9: 256–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Clozan; ***Chile***: Rize; ***Fr.***: Veratran; ***Ital.***: Rizen; Tienor; ***Jpn***: Rize; ***Spain***: Distensan.

Cloxazolam *(rINN)*

Cloxazolamum; CS-370; Kloksatsolaami; Kloxazolam; Клоксазолам.

10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

$C_{17}H_{14}Cl_2N_2O_2$=349.2

CAS — 24166-13-0.

ATC — N05BA22.

ATC Vet — QN05BA22.

UNII — GYL649Z0HY.

Pharmacopoeias. In *Jpn*.

Profile

Cloxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). A usual oral dose of 2 to 4 mg daily is given in divided doses for the short-term treatment of anxiety disorders (p. 1028.1); higher doses of up to 12 mg daily may be needed in some patients. A dose of 100 micrograms/kg may be used for premedication (see Anaesthesia, p. 1899.1).

References.

1. Ito M, *et al.* Cloxazolam treatment for patients with intractable epilepsy. *Pediatr Neurol* 2004; 30: 111–14.
2. Kimura N, *et al.* Initial and long-term effects of cloxazolam with intractable epilepsy. *Pediatr Neurol* 2010; 43: 403–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tolestan; ***Belg.***: Akton; ***Braz.***: Anoxolan; Cloxadil; Clozal; Elum; Eutonis; Olcadil; ***Jpn***: Sepazon; ***Port.***: Cloxam; Olcadil.

Clozapine *(BAN, USAN, rINN)*

Clozapin; Clozapina; Clozapinum; HF-1854; Klotsapiini; Klozapin; Klozapina; Klozapinas; Клозапин.

8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine.

$C_{18}H_{19}ClN_4$=326.8

CAS — 5786-21-0.

ATC — N05AH02.

ATC Vet — QN05AH02.

UNII — J60AR2IKIC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Clozapine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. It dissolves in dilute acetic acid.

USP 36: (Clozapine). A yellow crystalline powder. Insoluble in water; soluble in alcohol, in acetone, and in chloroform; sparingly soluble in acetonitrile.

Stability. A suspension of clozapine 100 mg in 5 mL, made by crushing clozapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for at least 18 days after preparation.[1]

1. Ramuth S, *et al.* A liquid clozapine preparation for oral administration in hospital. *Pharm J* 1996; 257: 190–1.

Uses and Administration

Clozapine is a dibenzodiazepine derivative and the prototype of the atypical antipsychotics. It has relatively weak dopamine receptor-blocking activity at D_1, D_2, D_3, and D_5 receptors but has a high affinity for the D_4 receptor. Clozapine possesses alpha-adrenergic blocking, antimuscarinic, antihistaminic, antiserotonergic, and sedative properties.

Clozapine is used for the management of schizophrenia (p. 1058.2); however, because of the risk of agranulocytosis, it is reserved for patients who fail to respond to other antipsychotics, including other atypicals, or who have severe neurological effects with such drugs. In the USA, it may also be used for reducing the risk of recurrent suicidal behaviour in those with schizophrenia or schizoaffective disorder who are at chronic risk for suicidal behaviour. In the UK, it is also used in the management of treatment-resistant psychoses associated with Parkinson's disease (p. 1058.1).

Clozapine use must be accompanied by strict procedures for the monitoring of white blood cell counts (see Precautions, p. 1060.3). To minimise the incidence of adverse effects, clozapine therapy should be introduced gradually, beginning with low doses and increasing according to response.

In the treatment of **schizophrenia**, including reducing the risk of suicidal behaviour, the usual oral dose is 12.5 mg once or twice on the first day followed by 25 mg once or twice on the second day. Thereafter the daily dosage may be increased gradually in steps of 25 to 50 mg to achieve a daily dose of up to 300 mg within 14 to 21 days (US licensed product information permits up to 450 mg daily by the end of 2 weeks). Subsequent increases in steps of 50 to 100 mg may be made once or twice weekly; a daily dosage of 900 mg should not be exceeded. Once a therapeutic response has been obtained (most patients respond to 200 to 450 mg daily), a gradual reduction of dosage to a suitable maintenance dose is recommended. The total daily dose is given in divided doses; a larger portion may be given at night. Daily maintenance doses of 200 mg or less may be given as a single dose in the evening. Although unlicensed in the UK for children and adolescents aged under 16 years, the *BNFC* suggests that those aged 12 years and over may be given the usual adult doses.

Elderly patients may require lower doses of clozapine and it is recommended that treatment should start with a dose of 12.5 mg on the first day and that subsequent dose increments should be restricted to 25 mg.

If clozapine is to be withdrawn, this should be done gradually over a 1- to 2-week period. However, immediate withdrawal with careful observation is essential if

neutropenia develops or if myocarditis or cardiomyopathy is suspected (see Precautions, p. 1060.3).

For patients who are restarting treatment after an interval of more than 2 days, 12.5 mg may be given once or twice on the first day. If this dose is well tolerated it may be possible to increase the dosage more quickly than when first starting. However, patients who have had respiratory or cardiac arrest with initial dosing, but were then successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after a break of even 24 hours. Additional monitoring of blood cell counts may also be required if treatment is interrupted, see Treatment Break, under Monitoring, p. 1061.2.

It is recommended that oral therapy with other antipsychotics should be withdrawn gradually before treatment with clozapine is started.

Clozapine has also been given by intramuscular injection.

In the management of treatment-resistant **psychoses in Parkinson's disease**, the initial oral dose of clozapine is no more than 12.5 mg once daily in the evening. Thereafter, the daily dosage may be increased in steps of 12.5 mg up to twice a week; a dose of 50 mg daily should not be reached before the end of the second week. The usual dose ranges from 25 to 37.5 mg daily. Increases in the daily dose above 50 mg should only be made in exceptional cases in steps of 12.5 mg at weekly intervals up to a maximum of 100 mg daily. The total daily dose should preferably be given as a single dose in the evening. Dosage of antiparkinsonian drugs may be increased when there has been complete remission of psychotic symptoms for at least 2 weeks with clozapine therapy. If psychotic symptoms recur after increases in antiparkinsonian therapy, the dose of clozapine may need to be increased in line with the above guidance. As in patients with schizophrenia, planned withdrawal of clozapine in patients with Parkinson's disease should also be gradual in steps of 12.5 mg over 1 to 2 weeks.

Action. Antipsychotics are thought to work through inhibition of dopamine D_2-receptors (see p. 1046.1), but this hypothesis fails to explain the activity of the atypical antipsychotics such as clozapine. How clozapine produces its antipsychotic activity is not clear; it has a high affinity for several different receptors.[1]

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; 164: 141–8.

Administration. There has been controversy over the bioequivalence or otherwise of different brands of clozapine. Although some reports indicate that it is perfectly possible to switch from branded to generic clozapine,[1-5] the need for monitoring and concerns about any requirement for retitration of doses (because of potential lack of bioequivalence[6]) have to be taken into account. There have been a few reports of exacerbation of psychotic symptoms in patients who were switched to a generic formulation.[7,8]

1. Sajbel TA, *et al.* Converting patients from brand-name clozapine to generic clozapine. *Ann Pharmacother* 2001; 35: 281–4.
2. Makela EH, *et al.* Branded versus generic clozapine for treatment of schizophrenia. *Ann Pharmacother* 2003; 37: 350–3.
3. Stoner SC, *et al.* A program to convert patients from trade-name to generic clozapine. *Pharmacotherapy* 2003; 23: 806–10.
4. Bazire S, Burton V. Generic clozapine in schizophrenia: what is all the fuss about? *Pharm J* 2004; 273: 720–1.
5. Oluboka O, *et al.* Does therapeutic equivalence follow bioequivalence? A randomized trial to assess clinical effects after switching from Clozaril to generic clozapine (Gen-Clozapine). *J Clin Pharmacol* 2010; 50: 531–5.
6. Lam YW, *et al.* Branded versus generic clozapine: bioavailability comparison and interchangeability issues. *J Clin Psychiatry* 2001; 62 (suppl 5): 18–22.
7. Kluznik JC, *et al.* Clinical effects of a randomized switch of patients from clozaril to generic clozapine. *J Clin Psychiatry* 2001; 62 (suppl 5): 14–17.
8. Mobeen R, Balter J. Case reports of the reemergence of psychotic symptoms after conversion from brand-name clozapine to a generic formulation. *Clin Ther* 2001; 23: 1720–31.

Administration in children. For details of uses and associated doses of clozapine in children and adolescents, see p. 1057.3.

Bipolar disorder. Clozapine is of benefit for the treatment of mania in patients with bipolar disorder (p. 397.2), and the use of atypical antipsychotics in the management of such patients is increasing. However, the adverse effects of clozapine may restrict its use.

Dementia. Although atypical antipsychotics such as clozapine have been tried in elderly patients with dementia, their use is associated with an increased risk of mortality in such patients; for further details, see under Risperidone, p. 1105.1. For further discussion of the management of disturbed behaviour, see p. 1030.2.

Parkinsonism. Clozapine is used as an alternative to classical antipsychotics in the management of **treatment-resistant psychoses** in patients with Parkinson's disease (p. 889.1). Some neurologists even consider clozapine to be the antipsychotic of choice in these patients,[1] although this remains to be determined. A review[2] in 1994 considered that there was little evidence to support clozapine as first choice given the quality of the available studies and the need for extensive monitoring. However, a subsequent double-blind, placebo-controlled study[3] showed that low-dose clozapine treatment (up to 50 mg daily) significantly improved drug-induced psychosis without worsening parkinsonism. Adverse effects noted in this study were generally mild, although in the clozapine group of 30 patients, there was 1 report of leucopenia. A similar study also reported benefit,[4] although 7 of 32 patients noted some aggravation of parkinsonism, usually mild and transient, while receiving clozapine. Adverse effects reported from other individuals have also included a patient with parkinsonism who had worsening of psychotic symptoms when her dose of clozapine was increased,[5] and the sudden return of psychosis in another patient with parkinsonism whose psychosis was successfully treated with clozapine for 5 years.[6]

Low-dose clozapine (about 40 mg daily) also appears to be of benefit in the management of **levodopa-induced dyskinesias** in patients with severe Parkinson's disease.[7]

1. Klein C, *et al.* Clozapine in Parkinson's disease psychosis: 5-year follow-up review. *Clin Neuropharmacol* 2003; 26: 8–11.
2. Pfeiffer C, Wagner ML. Clozapine therapy for Parkinson's disease and other movement disorders. *Am J Hosp Pharm* 1994; 51: 3047–53.
3. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; 340: 757–63.
4. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 1999; 353: 2041–2.
5. Auzou P, *et al.* Worsening of psychotic symptoms by clozapine in Parkinson's disease. *Lancet* 1994; 344: 955.
6. Greene P. Clozapine therapeutic plunge in patient with Parkinson's disease. *Lancet* 1995; 345: 1172–3.
7. Durif F, *et al.* Clozapine improves dyskinesias in Parkinson disease: a double-blind, placebo-controlled study. *Neurology* 2004; 62: 381–8.

Schizophrenia. Clozapine is an effective antipsychotic for the management of schizophrenia (p. 1031.3) but its use is limited by its haematotoxicity. Its efficacy and superiority over classical antipsychotics was shown in a multicentre study.[1] Patients refractory to at least 3 different antipsychotics and who failed to improve after a single-blind trial of haloperidol, were randomised, double-blind, to treatment for 6 weeks with either clozapine up to 900 mg daily, or chlorpromazine hydrochloride up to 1800 mg daily with benzatropine mesilate up to 6 mg daily. Of the 267 patients included in the evaluation, 5 of 141 (4%) improved with chlorpromazine and benzatropine, and 38 of 126 (30%) improved with clozapine. Clozapine was superior to chlorpromazine in the treatment of negative as well as positive symptoms. Reviews[2,3] of clozapine indicate that these findings have been replicated both in subsequent studies and in clinical practice; nevertheless, the authors of the later review[3] considered the data from the included studies to be weak and prone to bias. It is unclear for how long clozapine should be tried: although 1 study[4] identified new responses up to 12 months after starting therapy, others have indicated that if improvement was not seen within the first 6 to 24 weeks, it was unlikely to occur.[2,5]

Clozapine is also used to reduce suicide risk in patients with refractory chronic schizophrenia.[6] The reported suicide rate of 0.05% per year in 6300 patients in the UK given clozapine since 1990 was considered to be tenfold less than expected.[7] A subsequent study[8] found it to be more effective than olanzapine in preventing suicide attempts in patients with schizophrenia or schizoaffective disorder at high risk.

Clozapine has shown consistent clinical benefit in schizophrenic patients with persistent aggressive or violent behaviour.[2,9] Whether this is due to a sedative effect, a specific antiaggressive action, or just reflects an overall improvement in psychosis is unknown.

Clozapine has been advocated for use in schizophrenic patients with moderate to severe tardive dyskinesia. It is still unclear whether clozapine can itself cause tardive dyskinesia but some patients with established tardive dyskinesia have had improvement in their symptoms when using clozapine.[10,11]

1. Kane J, *et al.* Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45: 789–96.
2. Buckley PF. New dimensions in the pharmacologic treatment of schizophrenia and related psychoses. *J Clin Pharmacol* 1997; 37: 363–78. Correction. *ibid.* 1998; 38: 27.
3. Essali A, *et al.* Clozapine versus typical neuroleptic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2009 (accessed 04/06/09).
4. Meltzer HY, *et al.* A prospective study of clozapine in treatment-resistant schizophrenic patients I: preliminary report. *Psychopharmacology (Berl)* 1989; 99: S68–S72.
5. Conley RR, *et al.* Time to clozapine response in a standardized trial. *Am J Psychiatry* 1997; 154: 1243–7.
6. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry* 1995; 152: 183–90.
7. Kerwin RW. Clozapine: back to the future for schizophrenia research. *Lancet* 1995; 345: 1063–4.
8. Meltzer HY, *et al.* Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; 60: 82–91. Correction. *ibid.* 735.
9. Volavka J, *et al.* Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol* 2004; 24: 225–8.
10. Tamminga CA, *et al.* Clozapine in tardive dyskinesia: observations from human and animal model studies. *J Clin Psychiatry* 1994; 55 (suppl B): 102–6.
11. Nair C, *et al.* Dose-related effects of clozapine on tardive dyskinesia among "treatment-refractory" patients with schizophrenia. *Biol Psychiatry* 1996; 39: 529–30.

Adverse Effects and Treatment

Although clozapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary; antimuscarinic effects with clozapine may be more pronounced. Sedation and weight gain may also be more prominent. Clozapine can cause reversible neutropenia which may progress to a potentially fatal agranulocytosis; strict monitoring of white blood cell counts is essential (see Precautions, p. 1060.3). Eosinophilia may also occur. Anaemia, thrombocytopenia, and thrombocythaemia have been reported rarely.

Extrapyramidal disorders, including tardive dyskinesia, appear to be rare with clozapine. Clozapine has little effect on prolactin secretion. Clozapine appears to have a greater epileptic potential than chlorpromazine but a comparable risk of cardiovascular effects such as tachycardia and orthostatic hypotension. In rare cases, circulatory collapse with cardiac and respiratory arrest has occurred, and hypertension has also been reported. Clozapine is also associated with an increased risk of developing myocarditis that may, in rare cases, be fatal; cardiomyopathy and pericarditis have also been reported.

Additional adverse effects of clozapine include dizziness, hypersalivation (particularly at night), headache, nausea, vomiting, constipation (which, in a few cases, has led to gastrointestinal obstruction, faecal impaction, and paralytic ileus), urinary incontinence and retention, fatigue, and transient fever which must be distinguished from the signs of impending agranulocytosis. There have also been rare reports of dysphagia, parotid gland enlargement, confusion, delirium, thromboembolism, acute pancreatitis, hepatitis and cholestatic jaundice, and very rarely fulminant hepatic necrosis. Isolated cases of acute interstitial nephritis have been reported. Abnormalities of glucose homoeostasis and the onset of diabetes mellitus occur uncommonly; severe hyperglycaemia, sometimes leading to ketoacidosis or hyperosmolar coma, has been reported very rarely. There have also been rare reports of hypercholesterolaemia and hypertriglyceridaemia. Many of the adverse effects of clozapine are most common at the start of therapy and may be minimised by gradual increase in dosage.

Effects on the blood. Clozapine can cause reversible neutropenia which, if the drug is not withdrawn immediately may progress to a potentially fatal **agranulocytosis.** Particular concern over this adverse effect dates from 1975 when 17 cases of neutropenia or agranulocytosis, 8 of them fatal, were reported in Finland;[1] the calculated incidence[2] of agranulocytosis or severe granulocytopenia during this Finnish epidemic was 7.1 per 1000. These reports led to the withdrawal of clozapine in some countries or to restrictions in its use and intense haematological monitoring in others. After studies showing the efficacy of clozapine in severely ill schizophrenic patients unresponsive to adequate therapy with classical antipsychotics, the drug became available in the UK and USA in 1990 with strict procedures for monitoring of white blood cell counts. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[3] Clozapine was one of the individual drugs most frequently implicated, with 14 reports of agranulocytosis (1 fatal) and 119 of neutropenia (none fatal). Various estimates of the **incidence** of clozapine-associated agranulocytosis have been made; analysis of data from 11 555 patients given clozapine in the USA[4] showed a cumulative incidence of agranulocytosis of 8.0 per 1000 at 1 year and 9.1 per 1000 at 1½ years with the risk being increased in elderly patients. The majority of cases of agranulocytosis occurred within 3 months of the start of treatment with the risk peaking in the third month. The manufacturers reported a lower incidence of agranulocytosis of 4.8 per 1000 patients for the first 6 months[5] and an annual rate of 0.8 per 1000 patients during the next 2½ years. These figures were based on data on 56 000 patients in the USA given clozapine up to the end of March 1993. Analysis of data[6] on 6316 patients registered in the UK and Ireland between January 1990 and July 1994 to receive (although not necessarily given) clozapine produced a cumulative incidence of agranulocytosis of 0.7% during the first year and 0.8% over the whole study period. Most cases of agranulocytosis and neutropenia occurred during the first 6 to 18 weeks of treatment. The incidence of agranulocytosis (0.07%) and neutropenia (0.7%) seen during the second year of ther-

apy was of the same order of magnitude noted for some phenothiazine antipsychotics.

These data[6] and comparable data from the USA[7] were considered to indicate that mandatory haematological monitoring (see Precautions, p. 1060.3) helped to reduce the risks of clozapine-induced neutropenia and agranulocytosis and associated deaths.

The mechanism for clozapine-induced agranulocytosis is unclear and may be the result of direct toxicity or an immune response.[8,9] **Predisposing factors** for development of agranulocytosis have not been identified, apart from a possible excess of cases in female patients and an increased risk with increasing age. Furthermore, both agranulocytosis and neutropenia do not appear to be dose-related effects with clozapine. A postulated higher incidence of agranulocytosis in patients of Jewish background may be related to genetic factors.[10] Africans and Afro-Caribbeans appear to be at increased risk of developing neutropenia[6] and it has been noted[11] that many patients from these ethnic groups are currently already excluded from treatment with clozapine because their normal white blood cell and neutrophil counts are below the recommended range for treatment (see Monitoring under Precautions, p. 1061.1). However, UK licensed product information recommends that patients who have low white blood cell counts due to benign ethnic neutropenia may begin clozapine treatment with the agreement of a haematologist.

Evidence would suggest that development of clozapine-induced leucopenia or granulocytopenia precludes retreatment with clozapine at any future date; in a series of 9 re-treated patients, all developed leucopenia or agranulocytosis again.[12] In the USA, patients who have had clozapine withdrawn because of moderate leucopenia (judged to be when counts fall to 2000 to 3000 cells/mm^3) are considered eligible for a return to clozapine treatment when this count returns to normal; such patients are considered to have a five- or sixfold greater risk of agranulocytosis.[5]

1. Idänpään-Heikkilä J, *et al.* Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; **11**: 193–8.
2. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharmacol* 1977; **11**: 199–201.
3. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19**: 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Alvir JMJ, *et al.* Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993; **329**: 162–7.
5. Finkel MJ, Arellano F. White-blood-cell monitoring and clozapine. *Lancet* 1995; **346**: 849.
6. Atkin K, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169**: 483–8.
7. Honigfeld G, *et al.* Reducing clozapine-related morbidity and mortality: 5 years experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; **59** (suppl 3): 3–7.
8. Gerson SL, *et al.* Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* 1991; **338**: 262–3.
9. Hoffbrand AV, *et al.* Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; **7** (suppl 1): 1–60.
10. Leiberman JA, *et al.* HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990; **47**: 945–8.
11. Fisher N, Baigent B. Treatment with clozapine: black patients' low white cell counts currently mean that they cannot be treated. *BMJ* 1996; **313**: 1262.
12. Safferman AZ, *et al.* Rechallenge in clozapine-induced agranulocytosis. *Lancet* 1992; **339**: 1296–7.

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. However, a later review considered that there was overwhelming evidence that atypical antipsychotics induced more weight gain than classical antipsychotics.[2]

A separate review[3] calculated the average monthly weight gain associated with atypical antipsychotics to be:

- olanzapine (2.28 kg)
- zotepine (2.28 kg)
- quetiapine (1.76 kg)
- clozapine (1.72 kg)
- risperidone (0.96 kg)
- ziprasidone (0.80 kg)

A more recent review[4] of both short- (14 weeks or less) and long-term (6 months or more) studies noted that, out of all the atypicals considered, weight gain was greatest with olanzapine and clozapine, and the least with aripiprazole and ziprasidone. A review[5] of long-term (1 year or more) studies noted that although clozapine was associated with the highest risk of weight gain, and ziprasidone the lowest, the differences in risk with other atypicals were less intense when compared with findings from short-term studies which suggested the following decreasing order of weight-gain potential: clozapine, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, and ziprasidone.

Weight gain occurred most frequently during the first 6 to 12 months of treatment. It was recommended that if weight gain was more than 2 kg during the first 2 weeks, a strict dietary regimen should be started immediately. However, more recent opinion is that a change of antipsychotic may be necessary (see Effects on Carbohydrate Metabolism, below). Anti-obesity drugs have been tried although their routine use is not generally recommended.[2,6]

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156**: 1686–96.
2. Ananth J, *et al.* Atypical antipsychotic induced weight gain: pathophysiology and management. *Ann Clin Psychiatry* 2004; **16**: 75–85.
3. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Safety* 2001; **24**: 59–73.
4. Haddad P. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol* 2005; **19** (suppl): 16–27.
5. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. *Drug Safety* 2006; **29**: 303–19.
6. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; **62** (suppl 7): 22–31.

Effects on carbohydrate metabolism. Treatment with clozapine may be associated with an increased risk of glucose intolerance and diabetes mellitus; a similar association has also been noted for some other atypical antipsychotics.[1]

Data received by WHO indicated that up to December 2000, there had been 480 reports of glucose intolerance with clozapine, 253 with olanzapine, and 138 with risperidone.[2] In some cases weight gain was also reported, which may predispose to development of glucose intolerance. Other risk factors identified included an underlying diabetic condition, male gender, and use with some other medications including valproate, SSRIs, and buspirone. Regular monitoring of weight, blood glucose, and blood lipids was recommended in patients receiving clozapine, olanzapine, and risperidone.

Glucose intolerance has also been reported for the atypical antipsychotic quetiapine.[3,4]

Other reviewers have also found similar evidence of an increased risk of diabetes with atypical antipsychotics.[5,6] In September 2003 the FDA therefore requested labelling changes for all atypical antipsychotics to include the following recommendations and warnings:

- patients with diabetes mellitus receiving atypical antipsychotics should be monitored regularly for worsening glucose control
- patients with risk factors for diabetes mellitus should undergo fasting blood glucose testing at the start of, and during, treatment with atypical antipsychotics
- all patients given atypical antipsychotics should be monitored during treatment and those who develop hyperglycaemia should undergo fasting blood glucose testing
- in some cases hyperglycaemia resolved on withdrawal of the atypical antipsychotic but some patients needed antidiabetic therapy despite withdrawal

However, the American Diabetes Association and several other American medical associations[7] consider that the risks vary between atypical antipsychotics and have recommended that this should be taken into account when prescribing. The risk of weight gain, diabetes, and dyslipidaemia was considered to be greatest for clozapine and olanzapine, with risperidone and quetiapine having intermediate effects, and aripiprazole and ziprasidone having little effect (see also Effects on Body-Weight, above). They recommended that *baseline monitoring* should include:

- personal and family history of obesity, diabetes, dyslipidaemia, hypertension, or cardiovascular disease
- weight, height, and waist circumference
- blood pressure
- fasting blood glucose
- fasting lipid profile

Patients at risk for diabetes should receive an atypical drug with a lower propensity for weight gain and glucose intolerance. *Follow-up monitoring* should consist of reassessment of weight at 4, 8, and 12 weeks, and it was recommended that a change of antipsychotic should be considered for any patient who gained more than 5% of their original weight during treatment. Fasting plasma glucose and blood pressure should be assessed at 3 months and annually or more frequently thereafter according to risk. Lipid levels should also be assessed after 3 months and, if normal, at 5-year intervals thereafter. Any patient with worsening glycaemia or dyslipidaemia should be changed to an antipsychotic that has not been associated with significant weight gain or diabetes.

1. Melkersson K, Dahl M-L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs* 2004; **64**: 701–23.
2. Hedenmalm K, *et al.* Glucose intolerance with atypical antipsychotics. *Drug Safety* 2002; **25**: 1107–16.
3. Griffiths J, Springuel P. Atypical antipsychotics: impaired glucose metabolism. *Can Adverse Drug React News* 2001; **11** (4): 3–6. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v11n4-eng.pdf (accessed 21/08/08)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Atypical antipsychotics and hyperglycaemia. *Aust Adverse Drug React Bull* 2004; **23**: 11–12. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0406.htm (accessed 25/05/05)
5. Citrome LL, Jaffe AB. Relationship of atypical antipsychotics with development of diabetes mellitus. *Ann Pharmacother* 2003; **37**: 1849–57.
6. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005; **19** (suppl 1): 1–93.
7. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; **27**: 596–601. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/2/596.pdf (accessed 24/05/05)

Effects on the cardiovascular system. The UK CSM[1] issued a warning in November 1993 of the risk of myocarditis with clozapine. Three patients who died while taking clozapine had evidence of myocarditis. The CSM had also received one other report of myocarditis and one of cardiomyopathy associated with clozapine. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) subsequently reported[2] another 5 cases of clozapine-associated myocarditis in November 1994. A later report[3] from Australia identified 15 cases of myocarditis, including 5 fatalities, between January 1993 and March 1999 (these figures were established using both data from ADRAC and the Australian manufacturers). Between September 1989 and December 1999 the FDA had received reports of 28 cases of myocarditis (18 fatal) and 41 of cardiomyopathy (10 fatal) temporally associated with clozapine use.[4] A review[5] by the pharmacovigilance authorities in New Zealand stated that by November 1999 the manufacturers (*Novartis*) had analysed 125 reports of myocarditis received worldwide including 35 fatalities; 53% had occurred during the first month of treatment but about 5% occurred more than 2 years after starting treatment. A more recent review[6] of reports submitted to ADRAC between 1993 and 2003 identified 116 cases of myocarditis; of these, 60 patients were known to have recovered and 12 died. Myocarditis developed within a median of 17 days of starting clozapine therapy. In a reminder article,[7] the CSM has also commented that myocarditis occurs most commonly in the first 2 months whereas cardiomyopathy generally develops later in therapy. Pericarditis and pericardial effusions have also been reported. As myocarditis can be difficult to diagnose and confirmation is not always possible, the CSM recommended that if there was a high clinical suspicion of myocarditis, antipsychotic medication should be stopped. Presenting features might include persistent tachycardia at rest, heart failure, arrhythmia, or symptoms mimicking myocardial infarction or pericarditis. Patients who have developed clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

There is also evidence[8] that clozapine may be associated with fatal **thromboembolism.** Between February 1990 and December 1999, the FDA[9] had received 99 reports of venous thromboembolism associated with clozapine treatment. Of these reports, 83 mentioned pulmonary embolism with or without deep-vein thrombosis and 16 mentioned deep-vein thrombosis alone; 63 deaths were due to pulmonary embolism. The Swedish Adverse Reactions Advisory Committee had received reports[10] on 6 cases (5 fatal) of pulmonary embolism and 6 of venous thrombosis associated with clozapine treatment as of March 2000. The effect seemed to occur mainly in the first 3 months of treatment, and the majority of the cases involved men. However, analysis of data[11] from Germany and Switzerland suggests that the incidence of clozapine-associated thromboembolism is no different from that in psychiatric patients treated with classical antipsychotics or no antipsychotics at all.

For a discussion of **sudden unexpected deaths** associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

There have been isolated reports[12,13] of **paradoxical hypertension** in patients receiving clozapine. Use with atenolol has controlled the hypertension and allowed clozapine therapy to be continued.

Some studies[14] have suggested that serious cardiovascular effects might occur more frequently and might be more severe in healthy subjects given clozapine than in patients with schizophrenia. The manufacturers had therefore requested that pharmacokinetic studies of clozapine should be performed in patients with treatment-resistant schizophrenia rather than in healthy subjects.

For further details of effects of clozapine on the cardiovascular system, see Benzodiazepines under Interactions, p. 1062.1.

1. CSM/MCA. Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). *Current Problems* 1993; **19**: 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

2. Adverse Drug Reactions Advisory Committee (ADRAC). Clozapine and myocarditis. *Aust Adverse Drug React Bull* 1994; 13 (Nov): 14–15.
3. Kilian JG, *et al.* Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999; 354: 1841–5.
4. La Grenade L, *et al.* Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med* 2001; 345: 224–5.
5. New Zealand Medicines and Medical Devices Safety Authority. Potentially fatal complications of clozapine therapy: myocarditis, venous thromboembolism and constipation. Available at: http://www.medsafe.govt.nz/profs/puarticles/cloz1.htm (accessed 24/05/05)
6. Haas SJ, *et al.* Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Safety* 2007; 30: 47–57.
7. CSM/MCA. Clozapine and cardiac safety: updated advice for prescribers. *Current Problems* 2002; 28: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
8. Paciullo CA. Evaluating the association between clozapine and venous thromboembolism. *Am J Health-Syst Pharm* 2008; 65: 1825–9.
9. Knudson JP, *et al.* Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; 356: 252–3.
10. Hägg S, *et al.* Association of venous thromboembolism and clozapine. *Lancet* 2000; 355: 1155–6.
11. Wolstein J, *et al.* Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; 356: 252.
12. Gupta S. Paradoxical hypertension associated with clozapine. *Am J Psychiatry* 1994; 151: 148.
13. Ennis LM, Parker RM. Paradoxical hypertension associated with clozapine. *Med J Aust* 1997; 166: 278.
14. Pokorny R, *et al.* Normal volunteers should not be used for bioavailability or bioequivalence studies of clozapine. *Pharm Res* 1994; 11: 1221.

Effects on fluid and electrolyte homoeostasis. Hyponatraemia has been reported to be associated with clozapine,[1] as with other antipsychotics (p. 1048.3). It was emphasised that hyponatraemia should be excluded as a possible trigger when considering the epileptogenic potential of clozapine.

1. Ogilvie AD, Croy MF. Clozapine and hyponatraemia. *Lancet* 1992; 340: 672.

Effects on the gastrointestinal tract. The UK CSM had received 20 reports of serious gastrointestinal reactions resembling obstruction associated with clozapine treatment as of March 1999, of which 3 were fatal.[1] These reactions were thought to be due to the antimuscarinic actions of clozapine and, therefore, more likely to occur when clozapine was taken with other drugs with antimuscarinic actions such as tricyclic antidepressants, some antiparkinsonian drugs, and other antipsychotics; care was also warranted in those patients with a history of colonic disease or previous bowel surgery. It was also important to recognise and treat constipation in patients receiving clozapine to prevent the development of more serious complications such as obstruction and paralytic ileus. Subsequently, there have been continuing reports of serious gastrointestinal effects associated with clozapine-induced hypomotility, including bowel obstruction, ischaemia, and perforation.[2-5]

1. CSM/MCA. Clozapine (Clozaril) and gastrointestinal obstruction. *Current Problems* 1999; 25: 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023236&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
2. Palmer SE, *et al.* Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. *J Clin Psychiatry* 2008; 69: 759–68.
3. Leung JSY, *et al.* Rapidly fatal clozapine-induced intestinal obstruction without prior warning signs. *Aust N Z J Psychiatry* 2008; 42: 1073–4.
4. Hibbard KR, *et al.* Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. *Psychosomatics* 2009; 50: 416–19.
5. Martínez Díaz-Caneja C, *et al.* Severe bowel ischemia due to clozapine with complete remission after withdrawal. *J Clin Psychopharmacol* 2010; 30: 463–5.

Effects on the kidneys. Acute interstitial nephritis has been associated with clozapine treatment.[1-3] All 3 patients had acute renal failure which resolved when the drug was stopped. The authors of 1 report noted that the UK CSM had received 7 reports of acute renal failure associated with clozapine treatment, including 1 death, between December 1989 and February 1999.[2]

1. Elias TJ, *et al.* Clozapine-induced acute interstitial nephritis. *Lancet* 1999; 354: 1180–1.
2. Fraser D, Jibani M. An unexpected and serious complication of treatment with the atypical antipsychotic drug clozapine. *Clin Nephrol* 2000; 54: 78–80.
3. Au AF, *et al.* Clozapine-induced acute interstitial nephritis. *Am J Psychiatry* 2004; 161: 1501.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism, p. 1059.2.

Effects on the nervous system. As with other antipsychotics (see Convulsions, p. 1047.3), clozapine can lower the seizure threshold and cause EEG abnormalities, although treatment with clozapine appears to be associated with a higher frequency of seizures. A review[1] of 1418 patients treated with clozapine in the USA between 1972 and 1988 found that 41 had had generalised tonic-clonic seizures. It was considered that the risk of clozapine-induced seizures was dose-related. The seizure frequency was calculated to be:

- 1% at a dosage less than 300 mg daily
- 2.7% at 300 to 599 mg daily
- 4.4% with a dosage of 600 mg or more daily

Six of the patients had been taking other drugs reported to lower the seizure threshold. Therapy with clozapine was continued in 31 of the 41 patients by reducing the total daily dose of clozapine; antiepileptic drug therapy was begun in about half of the patients.

The UK CSM[2] considered that, although the epileptogenic effect of clozapine was claimed to be dose-related, the metabolism and plasma concentrations of clozapine were highly variable, and data from 8 cases reported to the CSM suggested that convulsions might possibly be related to high plasma concentrations in susceptible individuals. A low initial dosage followed by careful increases according to response and downward titration thereafter to a maintenance dose was recommended to avoid convulsions in susceptible individuals.

1. Devinsky O, *et al.* Clozapine-related seizures. *Neurology* 1991; 41: 369–71.
2. CSM. Convulsions may occur in patients receiving clozapine (Clozaril, Sandoz). *Current Problems* 31 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

Effects on the pancreas. There have been isolated reports of pancreatitis associated with clozapine therapy[1-3] and overdosage.[4] A systematic review[5] of the FDA's surveillance database and published case reports up to February 2002 found 192 patients who had pancreatitis (22 fatalities) after treatment with one or more antipsychotics. This included monotherapy with clozapine (72 patients), olanzapine (62 patients), risperidone (31 patients), and haloperidol (12 patients). Most cases occurred within 6 months of starting therapy.

1. Martin A. Acute pancreatitis associated with clozapine use. *Am J Psychiatry* 1992; 149: 714.
2. Frankenburg FR, Kando J. Eosinophilia, clozapine, and pancreatitis. *Lancet* 1992; 340: 251.
3. Garlipp P, *et al.* The development of a clinical syndrome of asymptomatic pancreatitis and eosinophilia after treatment with clozapine in schizophrenia: implications for clinical care, recognition and management. *J Psychopharmacol* 2002; 16: 399–400.
4. Jubert P, *et al.* Clozapine-related pancreatitis. *Ann Intern Med* 1994; 121: 722–3.
5. Koller EA, *et al.* Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. *Pharmacotherapy* 2003; 23: 1123–30.

Extrapyramidal disorders. Clozapine retains a place in therapy, despite its propensity to cause agranulocytosis, because, in part, of its reduced rate of extrapyramidal effects (see also p. 1049.2). Other drugs in the class have since been developed. However, although atypical antipsychotics carry a lower risk of causing extrapyramidal disorders, the risk is not zero; acute effects and tardive syndromes have been reported with these drugs, and the developing tendency to use them for high-dose therapy may perhaps narrow the margin of advantage.[1]

1. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. *Drug Safety* 2005; 28: 191–208.

Hypersalivation. Hypersalivation has been reported[1,2] to occur in up to 54% of patients receiving clozapine. The pathophysiology for this effect is unclear, but proposed mechanisms include action at muscarinic (M_3 and M_4) receptors, blockade of α_2-adrenoceptors, or distortion of the swallowing reflex. Management strategies have included chewing gum to increase frequency of swallowing or reduction of clozapine dosage in stabilised patients; antimuscarinics, including intranasal ipratropium, or α_2-agonists have been tried when other methods have failed. However, systemic antimuscarinics could potentially exacerbate the antimuscarinic adverse effects of clozapine. A recent systematic review[3] concluded that there are currently insufficient data to make any recommendations for treatment; the included studies had various limitations and a high risk of bias.

1. Davydov L, Botts SR. Clozapine-induced hypersalivation. *Ann Pharmacother* 2000; 34: 662–5.
2. Sockalingam S, *et al.* Clozapine-induced hypersalivation: a review of treatment strategies. *Can J Psychiatry* 2007; 52: 377–84.
3. Syed R, *et al.* Pharmacological interventions for clozapine-induced hypersalivation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 03/06/09).

Neuroleptic malignant syndrome. A review of the literature[1] suggested that clozapine may produce fewer extrapyramidal effects and a lower rise in creatine kinase concentrations than classical antipsychotics. The incidence of neuroleptic malignant syndrome (NMS—p. 1050.2) with clozapine appeared to be similar to that with classical antipsychotics;[1] however, its presentation may differ, with fever and rigidity less frequent, and possibly less severe, but diaphoresis more common.[2] Nevertheless, a later review[3] concluded that manifestations of NMS associated with the atypical antipsychotics clozapine, olanzapine, quetiapine, and risperidone were of similar nature and severity to those associated with classical antipsychotics. NMS has also been reported[4] with the use of amisulpride and aripiprazole.

Use of the atypical antipsychotics aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone has been associated with case reports of NMS in children and adolescents aged 11 to 18 years; symptoms were consistent with those seen in adults.[5]

1. Sachdev P, *et al.* Clozapine-induced neuroleptic malignant syndrome: a review and report of new cases. *J Clin Psychopharmacol* 1995; 15: 365–71.
2. Karagianis JL, *et al.* Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. *Ann Pharmacother* 1999; 33: 623–30. Correction. *ibid.*; 1011.
3. Ananth J, *et al.* Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004; 65: 464–70.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Aripiprazole and neuroleptic malignant syndrome. *Aust Adverse Drug React Bull* 2007; 26: 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0704.pdf (accessed 03/04/08)
5. Croarkin PE, *et al.* Neuroleptic malignant syndrome associated with atypical antipsychotics in pediatric patients: a review of published cases. *J Clin Psychiatry* 2008; 69: 1157–65.

Withdrawal. Abrupt withdrawal of clozapine may be associated with symptoms that have been described as 'cholinergic rebound' although the manifestations, which may include headache, profuse sweating, hypersalivation, bronchoconstriction, agitation, enuresis, and diarrhoea also have some common features with the serotonin syndrome (p. 443.2); motor disorders and exacerbation of extrapyramidal disorders have also occurred. In addition, as with other antipsychotics, abrupt withdrawal of clozapine may be associated with rapid relapse of the original psychosis. In a retrospective case-note study of 29 schizophrenic patients whose clozapine treatment was withdrawn, abrupt withdrawal in 20 resulted in a marked, immediate deterioration in their mental state.[1] Of 3 further patients who had delirium with psychotic symptoms shortly after stopping clozapine, symptoms developed in 1 within 24 hours despite gradual withdrawal of clozapine over a 2-week period.[2] All the patients responded rapidly to resumption of low doses of clozapine.

1. Baker M, White T. Life after clozapine. *Med Sci Law* 2004; 44: 217–21.
2. Stanilla JK, *et al.* Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin Psychiatry* 1997; 58: 252–5.

Precautions

Clozapine should not be given to patients with uncontrolled epilepsy, alcoholic or toxic psychoses, drug intoxication, or a history of circulatory collapse. It should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. It is contra-indicated in patients with bone-marrow suppression, myeloproliferative disorders, or any abnormalities of white blood cell count or differential blood count. It is also contra-indicated in patients with a history of drug-induced neutropenia or agranulocytosis with the exception of that due to chemotherapy. It should not be used with drugs that carry a high risk of bone-marrow suppression (see Interactions, p. 1061.2).

Clozapine is contra-indicated in patients with severe renal impairment; caution is required in mild to moderate renal impairment. It should be used with caution in hepatic impairment and avoided in symptomatic or progressive liver disease or hepatic failure. Patients with a history of cardiac impairment or abnormal cardiac findings on examination should be referred to a specialist for further evaluation, which may include an ECG; treatment with clozapine should only then be started if the potential benefits clearly outweigh any risk. Clozapine should not be used in severe heart failure.

Clozapine possesses antimuscarinic properties and consequently it is contra-indicated in patients with paralytic ileus; it should also be used with caution in benign prostatic hyperplasia and angle-closure glaucoma.

Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes (see Effects on Carbohydrate Metabolism, p. 1059.2).

Monitoring the white blood cell and absolute neutrophil counts is mandatory during clozapine treatment and should be carried out in accordance with official recommendations; these may vary between countries (see Monitoring, p. 1061.1 for further details). Patients or their carers should report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.

Patients who develop tachycardia at rest, dyspnoea, arrhythmias, chest pain, or other signs and symptoms of heart failure should be investigated immediately and clozapine treatment stopped if a diagnosis of myocarditis or cardiomyopathy is suspected.

Because of an increased risk of collapse due to orthostatic hypotension associated with rapid dose escalation during initial titration of clozapine dosage, it is recommended that treatment should be begun under close medical supervision. In addition, patients with Parkinson's disease should have

their blood pressure monitored for the first weeks of treatment.

On planned withdrawal, the dose of clozapine should be reduced gradually over at least a 1- to 2-week period in order to avoid the risk of rebound psychosis and other withdrawal symptoms (see p. 1060.3). If abrupt withdrawal is necessary then patients should be observed carefully.

Clozapine may affect the performance of skilled tasks such as driving.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of clozapine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Clozapine appears to be distributed into breast milk in relatively high concentrations.[2] Concentrations in a patient given 50 mg daily were 63.5 nanograms/mL in breast milk and 14.7 nanograms/mL in plasma; at 100 mg daily they were 115.6 nanograms/mL and 41.4 nanograms/mL, respectively.

The manufacturers have also stated that studies in *animals* suggest that clozapine is excreted into breast milk and has an effect on nursing infants; they recommend that mothers receiving clozapine should not breast feed.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/05)
2. Barnas C, *et al.* Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. *Am J Psychiatry* 1994; **151**: 945.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Monitoring. *WHITE CELL COUNTS.* A white blood cell count and a differential blood count *must* be performed before the start of, and during, clozapine therapy. Treatment should not be started if the white blood cell count is less than 3500 cells/mm^3 and the absolute neutrophil count (ANC) is less than 2000 cells/mm^3, or if there is an abnormal differential count. Monitoring should continue throughout therapy and for 4 weeks after withdrawal.

In the EU, including the UK, monitoring is performed at weekly intervals for the first 18 weeks and then at least every 2 weeks between weeks 18 and 52; after 1 year of treatment with stable neutrophil counts, patients may be monitored at least every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 or the ANC falls to between 1500 and 2000 cells/mm^3 then monitoring should be performed at least **twice weekly** until values stabilise or increase.
- Clozapine should be **withdrawn** immediately if the white blood cell count falls below 3000 cells/mm^3 or the ANC drops below 1500 cells/mm^3; counts should be monitored daily until they return to normal. Clozapine should not be restarted in these patients.

In the USA, white blood cell and ANC are monitored weekly for the first 6 months and then every 2 weeks thereafter; after 1 year of therapy, patients may be monitored every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 and the ANC is above 1500 cells/mm^3 then monitoring should be performed **twice weekly**.
- If the white blood cell count falls below 3000 cells/mm^3 or the ANC is below 1500 cells/mm^3 then clozapine treatment should be **interrupted** and counts performed daily initially. Clozapine may be restarted if the white blood cell count recovers to above 3500 cells/mm^3 and the ANC to above 2000 cells/mm^3. After recovery, weekly monitoring is recommended for the next 12 months before reducing to every 2 weeks for 6 months, and then every 4 weeks thereafter.
- Clozapine should be **withdrawn** if the white blood cell count falls below 2000 cells/mm^3 or the ANC drops below 1000 cells/mm^3; counts should be monitored daily, initially, until they return to normal. Clozapine should not be restarted in these patients.

In patients with decreased white blood cell or ANC it is especially important that they or their carers report the development of any infection or signs such as fever, sore throat, or flu-like symptoms that suggest infection.

EOSINOPHIL COUNT. In the EU, clozapine should be withdrawn if the eosinophil count is greater than 3000 cells/mm^3; it should only be restarted once the count has fallen to below 1000 cells/mm^3.

Similar advice is given in US licensed product information although the values differ: clozapine should be withdrawn if the eosinophil count is above 4000 cells/mm^3 and restarted once the count has fallen to below 3000 cells/mm^3.

PLATELET COUNT. European licensing information states that clozapine should be stopped if the platelet count falls below 50 000 cells/mm^3.

TREATMENT BREAK. If treatment with clozapine is interrupted for reasons other than abnormal haematological values then more frequent monitoring may be required following resumption of therapy.

In the EU, patients who have taken clozapine for at least 18 weeks and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 4 weeks if the counts are stable; a break of 4 weeks or more would require weekly monitoring for the next 18 weeks.

US licensed product information recommends resuming weekly monitoring for 6 months in all patients whose therapy has been interrupted for more than 1 month; frequency of monitoring is then reduced as described in White Cell Counts, see above. Those who have taken clozapine for at least 6 months and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 2 weeks for 6 months if the counts are stable; those on clozapine for over 1 year may be monitored every 4 weeks after initial weekly monitoring for 6 weeks.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clozapine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. A review of the literature[1] between 1993 and April 2004 suggested that clozapine and olanzapine do not appear to increase the risk of fetal teratogenicity; literature regarding aripiprazole, quetiapine, risperidone, and ziprasidone was incomplete or not available. The rate of spontaneous abortions in pregnant women exposed to clozapine or olanzapine was not found to be higher than that of the general population; however, these 2 drugs increased the risk of hyperglycaemia in pregnant women. A prospective comparative study[2] of pregnancy outcomes in women taking clozapine, olanzapine, quetiapine, and risperidone also concluded that atypicals do not appear to be associated with an increased risk for major malformations when compared with the baseline risk in the general population. The authors recommended that benefits and risks be weighed carefully in each case and optimal control of the psychiatric disorder be maintained throughout pregnancy and postpartum together with careful monitoring.

1. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. *Ann Pharmacother* 2004; **38**: 1265–71.
2. McKenna K, *et al.* Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 2005; **66**: 444–9.

Interactions

Clozapine may enhance the central effects of MAOIs and CNS depressants including alcohol, antihistamines, benzodiazepines, and opioid analgesics.

Clozapine should not be used with drugs that carry a high risk of bone-marrow suppression including carbamazepine, co-trimoxazole, chloramphenicol, penicillamine, sulfonamides, antineoplastics, or pyrazolone analgesics such as azapropazone. Long-acting depot antipsychotics have myelosuppressive potential and should not be used with clozapine as they cannot be withdrawn rapidly should neutropenia occur. Additive effects may occur when clozapine is given with drugs that possess antimuscarinic, hypotensive, or respiratory depressant effects. Clozapine may reduce the effects of alpha-adrenoceptor agonists such as noradrenaline.

The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit or act as a substrate to this isoenzyme may affect plasma concentrations of clozapine and the dose of clozapine may need to be altered. Increased plasma-clozapine concentrations, with an increased risk of adverse effects, may be seen in patients who suddenly stop smoking. Use with phenytoin or other enzyme-inducing drugs may accelerate the metabolism of clozapine and reduce its plasma concentrations.

References.

1. Taylor D. Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 1997; **171**: 109–12.

Antibacterials. A patient with schizophrenia controlled with clozapine therapy had a tonic-clonic seizure 7 days after starting treatment with *erythromycin*.[1] It appeared that erythromycin had inhibited the metabolism of clozapine and raised its serum concentrations. Increased drowsiness and hypersalivation have been seen in a patient receiving clozapine and *ampicillin*; he recovered when ampicillin was replaced with doxycycline.[2]

Giving clozapine with *rifampicin* has resulted in decreased clozapine concentrations with consequent return of paranoid thoughts in a patient with a complicated history of schizophrenia.[3] An improvement was seen after rifampicin was replaced with ciprofloxacin. The interaction was thought to be due to the induction of cytochrome P450 isoenzymes, particularly CYP1A2, by rifampicin, resulting in the accelerated metabolism of clozapine.

1. Funderburg LG, *et al.* Seizure following addition of erythromycin to clozapine treatment. *Am J Psychiatry* 1994; **151**: 1840–1.
2. Csík V, Molnár J. Possible adverse interaction between clozapine and ampicillin in an adolescent with schizophrenia. *J Child Adolesc Psychopharmacol* 1994; **4**: 123–8.
3. Joos AAB, *et al.* Pharmacokinetic interaction of clozapine and rifampicin in a forensic patient with atypical mycobacterial infection. *J Clin Psychopharmacol* 1998; **18**: 83–5.

Antidepressants. Rises in serum concentrations of clozapine have been found in patients receiving clozapine after addition of *fluoxetine*[1] or *fluvoxamine*[2] to therapy. Increased serum concentrations of clozapine have also been reported when *paroxetine* or *sertraline* was added to therapy.[3] A possible serotonin syndrome (p. 443.2) has been reported[4] in a patient receiving *clomipramine* after clozapine was gradually withdrawn from the treatment regimen, although the symptoms were also similar to those of clozapine withdrawal (see p. 1060.3). There has been an isolated report[5] of a patient who developed myoclonic jerks 79 days after fluoxetine was added to treatment with clozapine and lorazepam, although some[6] doubt whether the effects were entirely due to an interaction. Giving clozapine with *lithium* may increase the risk of neuroleptic malignant syndrome. For reference to neurological reactions in patients receiving lithium with clozapine, see p. 431.3.

1. Centorrino F, *et al.* Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151**: 123–5.
2. Jerling M, *et al.* Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994; **16**: 368–74.
3. Centorrino F, *et al.* Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996; **153**: 820–2.
4. Zerjav-Lacombe S, Dewan V. Possible serotonin syndrome associated with clomipramine after withdrawal of clozapine. *Ann Pharmacother* 2001; **35**: 180–2.
5. Kingsbury SJ, Puckett KM. Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152**: 473.
6. Baldessarini RJ, *et al.* Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152**: 473–4.

Antiepileptics. Use of *phenytoin* or other *enzyme-inducing antiepileptics* may accelerate the metabolism of clozapine and reduce its plasma concentrations. Studies have found that addition of *sodium valproate* to clozapine therapy may increase[1] or decrease[2] plasma concentrations of clozapine. Although no increase in clozapine-related adverse effects or loss of control of psychotic symptoms were reported in these studies, there has been a report[3] of a patient who developed sedation, confusion, slurring of speech and other functional impairment after valproate was given with clozapine.

See also under Benzodiazepines, p. 1062.1.

1. Centorrino F, *et al.* Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151**: 123–5.
2. Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. *Biol Psychiatry* 1994; **36**: 487–8.
3. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol* 1995; **15**: 139–41.

Antipsychotics. Giving *risperidone* to a patient with schizoaffective disorder partially controlled by clozapine produced clinical improvement but was associated with a 74% rise in serum-clozapine concentrations over a 2-week period.[1] Although no adverse effects occurred in this patient, the potential for serious adverse effects requires caution if these drugs are used together. Neuroleptic malignant syndrome associated with use of clozapine with *haloperidol* has been reported.[2]

See also under Chlorpromazine, p. 1053.1.

1. Tyson SC, *et al.* Pharmacokinetic interaction between risperidone and clozapine. *Am J Psychiatry* 1995; **152**: 1401–2.
2. Garcia G, *et al.* Neuroleptic malignant syndrome with antidepressant/antipsychotic drug combination. *Ann Pharmacother* 2001; **35**: 784–5.

Antivirals. Although UK licensed product information for *ritonavir* states that it may increase plasma concentrations of clozapine with a resultant increase in the risk of toxicity, there is evidence to suggest that, in fact, ritonavir may decrease the plasma concentrations of clozapine.[1] Ritonavir has been noted to induce the cytochrome P450 isoenzyme CYP1A2 and hence, as clozapine is mainly

metabolised via this isoenzyme, an acceleration of the metabolism of clozapine would be expected.

1. Penzak SR, *et al.* Comment: significant interactions with new antiretrovirals and psychotropic drugs. *Ann Pharmacother* 1999; 33: 1372–3.

Benzodiazepines. Concern has been expressed over reports of cardiorespiratory collapse in patients taking both clozapine and benzodiazepines.[1,2] In response, the manufacturers of clozapine outlined[3] similar cases reported to them in the USA. Of 7 cases of respiratory arrest or depression only 2 involved recent use of a benzodiazepine; among 26 cases of orthostatic hypotension with syncope reported during the first year the drug was marketed, only 8 included recent benzodiazepine use. The manufacturers concluded that an increased risk of such reactions in patients taking both drugs simultaneously was possible but not established, and advised caution when starting clozapine therapy in patients taking benzodiazepines.

Hypersalivation associated with clozapine and benzodiazepines may be exacerbated when these drugs are used together. A patient[4] had increased hypersalivation, salivary thickening, and distension of the parotid glands when *clonazepam* was added to treatment with clozapine. Adverse effects reported in 5 other patients given clozapine with benzodiazepines included hypersalivation, sedation, ataxia, and symptoms of delirium.[5,6]

1. Sassim N, Grohmann R. Adverse drug reactions with clozapine and simultaneous application of benzodiazepines. *Pharmacopsychiatry* 1988; 21: 306–7.
2. Friedman LJ, *et al.* Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; 325: 518.
3. Pinkel MJ, Schwimmer JL. Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; 325: 518–19.
4. Martin SD. Drug-induced parotid swelling. *Br J Hosp Med* 1993; 50: 426.
5. Cobb CD, *et al.* Possible interaction between clozapine and lorazepam. *Am J Psychiatry* 1991; 148: 1606–7.
6. Jackson GW, *et al.* Delirium associated with clozapine and benzodiazepine combinations. *Ann Clin Psychiatry* 1995; 7: 139–41.

Buspirone. Potentially fatal gastrointestinal bleeding, accompanied by severe acidosis and hyperglycaemia, developed in a patient given buspirone with clozapine.[1] The patient had previously been taking clozapine for over a year without adverse effect, and was subsequently maintained on clozapine alone without a recurrence of symptoms.

1. Good ML Lethal interaction of clozapine and buspirone? *Am J Psychiatry* 1997; 154: 1472–3.

Gastrointestinal drugs. A patient stabilised on clozapine developed increased serum clozapine concentrations and signs of clozapine toxicity after starting treatment with *cimetidine*.[1] Cimetidine was withdrawn and ranitidine substituted without recurrence of toxicity.

A marked reduction in plasma-clozapine concentrations was seen in 2 smokers stabilised on the antipsychotic who began treatment with *omeprazole*,[2] a known inducer of the cytochrome P450 isoenzyme CYP1A2. However, a small retrospective analysis of the effect of stopping omeprazole in 13 patients taking both drugs suggested that the effect of omeprazole was only significant in non-smokers, and the clozapine dose did not need to be adjusted in any of these patients.[3]

1. Szymanski S, *et al.* A case report of cimetidine-induced clozapine toxicity. *J Clin Psychiatry* 1991; 52: 21–2.
2. Frick A, *et al.* Omeprazole reduces clozapine plasma concentrations: a case report. *Pharmacopsychiatry* 2003; 36: 121–3.
3. Mookhoek EJ, Loonen AJ. Retrospective evaluation of the effect of omeprazole on clozapine metabolism. *Pharm World Sci* 2004; 26: 180–2.

Xanthines. *Caffeine* may inhibit the metabolism of clozapine.[1,2] Care should be taken before stopping or starting caffeine-containing beverages in patients stabilised on clozapine treatment.

1. Carrillo JA, *et al.* Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* 1998; 18: 311–16.
2. Hägg S, *et al.* Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2000; 49: 59–63.

Pharmacokinetics

Although clozapine is well absorbed from the gastrointestinal tract, its bioavailability is limited to about 50% by first-pass metabolism. Peak plasma concentrations occur, on average, about 2.5 hours after oral doses. Clozapine is about 95% bound to plasma proteins and has a mean terminal elimination half-life of about 12 hours at steady state. It is almost completely metabolised and routes of metabolism include *N*-demethylation, hydroxylation, and *N*-oxidation; the desmethyl metabolite (norclozapine) has limited activity. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the faeces. There is wide interindividual variation in plasma concentrations of clozapine and no simple correlation has been found between plasma concentrations and therapeutic effect. It is distributed into breast milk.

References.
1. Jann MW, *et al.* Pharmacokinetics and pharmacodynamics of clozapine. *Clin Pharmacokinet* 1993; 24: 161–76.
2. Lin S-K, *et al.* Disposition of clozapine and desmethylclozapine in schizophrenic patients. *J Clin Pharmacol* 1994; 34: 318–24.
3. Freeman DJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in clozapine therapy? *Clin Pharmacokinet* 1997; 32: 93–100.
4. Olesen OV. Therapeutic drug monitoring of clozapine treatment: therapeutic threshold value for serum clozapine concentrations. *Clin Pharmacokinet* 1998; 34: 497–502.
5. Guitton C, *et al.* Clozapine and metabolite concentrations during treatment of patients with chronic schizophrenia. *J Clin Pharmacol* 1999; 39: 721–8.
6. Dettling M, *et al.* Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. *Psychopharmacology (Berl)* 2000; 152: 80–6.
7. Renwick AC, *et al.* Monitoring of clozapine and norclozapine plasma concentration-time curves in acute overdose. *J Toxicol Clin Toxicol* 2000; 38: 325–8.
8. Frazier JA, *et al.* Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. *J Clin Psychopharmacol* 2003; 23: 87–91.
9. Tang Y-L, *et al.* Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. *Br J Clin Pharmacol* 2007; 64: 49–56.

Bioavailability. Mean plasma concentration of clozapine increased from 329 to 629 nanograms/mL in 10 patients when switched from an extemporaneous liquid formulation to conventional tablets.[1]

1. Coker-Adeyemi F, Taylor D. Clozapine plasma levels in patients switched from clozapine liquid to tablets. *Pharm J* 2002; 269: 650–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lapenax; Sequax; *Austral.*: Clopine; Clozaril; *Austria*: Lanolept; Leponex; *Belg.*: Leponex; *Braz.*: Leponex; Pinazan; *Canad.*: Clozaril; *Chile*: Dicomex; Leponex; *Cz.*: Leponex; *Denm.*: Cloment†; Leponex; *Fin.*: Froidir; Leponex; *Fr.*: Leponex; *Ger.*: Elcrit; Leponex; *Gr.*: Leponex; *Hong Kong*: Clozaril; *Hung.*: Leponex; *India*: Chrozap; Clomach; Clopaz; Cozacin; Lozapin; Lozaril; Sizopin; *Indon.*: Clopine; Clorilex; Clozaril; Luften; Sizoril; *Irl.*: Clozalux; Clozaril; Denzapine; *Israel*: Leponex; Lozapine; *Ital.*: Leponex; *Jpn*: Clozaril; *Malaysia*: Anzapine; Clozarem; Clozaril; Zapine; *Mex.*: Clopsine; Leponex; *Neth.*: FazaClo†; Leponex; *Norw.*: Leponex; *NZ*: Clopine; Clozaril; *Philipp.*: Ihope; Leponex; Syclop; Ziproc; *Pol.*: Klozapol; Leponex; *Port.*: Leponex; Ozapim; *Rus.*: Azaleptin (Азалептин); Closastene (Клозастен); Leponex (Лепонекс); *S. Afr.*: Clomen; Leponex; *Singapore*: Clozaril; *Spain*: Leponex; Nemea; *Swed.*: Leponex; *Switz.*: Clopin; Leponex; *Thai.*: Cloril; Clozamed; Clozaril; *Turk.*: Clonex; Leponex; *UK*: Clozaril; Denzapine; Zaponex; *Ukr.*: Azapin (Азапин); Leponex (Лепонекс); *USA*: Clozaril; FazaClo; Versacloz; *Venez.*: Leponex.

Pharmacopoeial Preparations
BP 2014: Clozapine Oral Suspension;
USP 36: Clozapine Tablets.

Cyamemazine *(rINN)*

Ciamemazina; Cyamémazine; Cyamemazinum; Cyamepromazine; RP-7204; Циамемазин.
10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile.
$C_{19}H_{21}N_3S$=323.5
CAS — 3546-03-0 (cyamemazine); 93841-82-8 (cyamemazine tartrate).
ATC — N05AA06.
ATC Vet — QN05AA06.
UNII — A2JGV5CNU4.

Profile

Cyamemazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It is used in the management of a variety of psychiatric disorders including anxiety disorders (p. 1028.1) and aggressive behaviour (p. 1030.2).

Cyamemazine has been given orally as the base or the tartrate and by injection as the base. Doses are expressed in terms of the base; cyamemazine tartrate 36.6 mg is equivalent to about 25 mg of cyamemazine. Oral doses have ranged from 25 to 300 mg daily, depending on the individual and the condition being treated; the daily dosage is given in 2 or 3 divided doses. Up to 600 mg daily has been given orally in severe or resistant psychoses. Doses given by intramuscular injection have ranged from 25 to 200 mg daily.

Cyamemazine should be given in reduced dosage to elderly patients; the parenteral route is not recommended for the elderly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Tercian; *Port.*: Tercian.

Cyclobarbital *(BAN, rINN)*

Ciclobarbital; Cyclobarbitalum; Cyclobarbitone; Cyklobarbital; Ethylhexabital; Hexemalum; Syklobarbitaali; Циклобарбитал.
5-(Cyclohex-1-enyl)-5-ethylbarbituric acid.
$C_{12}H_{16}N_2O_3$=236.3
CAS — 52-31-3.
ATC — N05CA10.
ATC Vet — QN05CA10.
UNII — 0M8A98AD9H.

NOTE. The name ciclobarbital has sometimes been applied to hexobarbital.

Cyclobarbital Calcium *(BANM, rINNM)*

Calcii Cyclobarbitalum; Ciclobarbital cálcico; Ciclobarbital Calcium; Cyclobarbital Calcique; Cyclobarbitalum Calcicum; Cyclobarbitone Calcium; Cyklobarbital wapniowy; Hexemalcalcium; Кальций Циклобарбитал.
Calcium 5-(cyclohex-1-enyl)-5-ethylbarbiturate.
$(C_{12}H_{15}N_2O_3)_2Ca$=510.6
CAS — 5897-20-1.
ATC — N05CA10.
ATC Vet — QN05CA10.
UNII — 0HZN7FV25R.

Pharmacopoeias. In *Pol.*

Profile

Cyclobarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). The calcium salt has been used as a hypnotic but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Reladorm (Реладорм).

Delorazepam *(pINN)*

Chlordesmethyldiazepam; Clordesmethyldiazepam; Délorazépam; Delorazepamum; Делоразепам.
7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.
$C_{15}H_{10}Cl_2N_2O$=305.2
CAS — 2894-67-9.
UNII — O91W32476G.

Profile

Delorazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been used in the short-term treatment of anxiety disorders (p. 1028.1) in oral doses of 0.5 to 2 mg given 2 or 3 times daily. An oral dose of 0.5 to 2 mg has also been given at night for insomnia (p. 1033.2). The drug has also been given parenterally.

Administration in hepatic or renal impairment. The pharmacokinetics of total delorazepam were unchanged in patients with renal failure undergoing haemodialysis compared with controls.[1] However, the apparent volume of distribution of unbound drug was smaller and the clearance slower. The volume of distribution and clearance of unchanged drug was also reduced in patients with liver disease.[2]

1. Sennesael J, *et al.* Pharmacokinetics of intravenous and oral chlordesmethyldiazepam in patients on regular haemodialysis. *Eur J Clin Pharmacol* 1991; 41: 65–8.
2. Bareggi SR, *et al.* Effects of liver disease on the pharmacokinetics of intravenous and oral chlordesmethyldiazepam. *Eur J Clin Pharmacol* 1995; 48: 265–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Dadumir; En.

Detomidine Hydrochloride

(BANM, USAN, rINNM)

Detomidini Hydrochloridum; Detomidiinihydrokloridi; Detomidin hydrochlorid; Detomidina, hidrocloruro de; Détomidine, chlorhydrate de; Detomidin-hidroklorid; Detomidinhydroklorid; Detomidini Hydrochloridum; Hidrocloruro de detomidina; MPV-253-All; Детомидина Гидрохлорид.
4-(2,3-Dimethylbenzyl)imidazole hydrochloride.
$C_{12}H_{14}N_2$,HCl=222.7

CAS — 76631-46-4 (detomidine); 90038-01-0 (detomidine hydrochloride).
UNII — 95K4LKB6QE.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Detomidine Hydrochloride for Veterinary Use; Detomidi Hydrochloride BP(Vet) 2014). A white or almost white, hygroscopic, crystalline powder. Soluble in water; freely soluble in alcohol; practically insoluble in acetone; very slightly soluble in dichloromethane. Protect from moisture.

Profile

Detomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Dexmedetomidine Hydrochloride *(BANM, USAN, rINNM)*

Deksmedetomidin Hidroklorür; Dexmedetomidina, hidrocloruro de; Dexmédétomidine, Chlorhydrate de; Dexmedetomidini Hydrochloridum; Hidrocloruro de dexmedetomidina; MPV-1440 (dexmedetomidine); Дексмедетомидина Гидрохлорид.

(*S*)-4-[1-(2,3-Xylyl)ethyl]imidazole hydrochloride.

$C_{13}H_{16}N_2$,HCl=236.7

CAS — 113775-47-6 (dexmedetomidine); 145108-58-3 (dexmedetomidine hydrochloride).
ATC — N05CM18.
ATC Vet — QN05CM18.
UNII — 1018WH7F9I.

Uses and Administration

Dexmedetomidine is a selective alpha$_2$-adrenergic receptor agonist with anxiolytic, analgesic, and sedative properties. It is used for the sedation (p. 1032.2) of mechanically ventilated patients in intensive care and of non-intubated patients in surgical and medical procedures. Dexmedetomidine is given as the hydrochloride, but doses are expressed in terms of the base. Dexmedetomidine hydrochloride 118 micrograms is equivalent to about 100 micrograms of dexmedetomidine.

It is diluted to a concentration of 4 micrograms/mL in sodium chloride 0.9% before use and is given by intravenous infusion in a loading dose equivalent to 1 microgram/kg of dexmedetomidine over 10 minutes. This is followed by a maintenance infusion of 200 to 700 nanograms/kg per hour for up to 24 hours when used in intensive care settings. For use in procedural sedation, the loading dose is followed by a maintenance infusion of 0.2 to 1 micrograms/kg per hour; lower loading doses may be required for less invasive procedures. Reduced doses may be necessary in patients with hepatic impairment or in the elderly.

The racemate, medetomidine (p. 1083.2), is used as the hydrochloride in veterinary medicine.

References.

1. Venn RM, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999; **54:** 1136–42.
2. Bhana N, *et al.* Dexmedetomidine. *Drugs* 2000; **59:** 263–8.
3. Coursin DB, *et al.* Dexmedetomidine. *Curr Opin Crit Care* 2001; **7:** 221–6.
4. Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. *Neurosurgery* 2005; **57** (suppl): 1–10.
5. Szumita PM, *et al.* Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. *Am J Health-Syst Pharm* 2007; **64:** 37–44.
6. Pandharipande PP, *et al.* Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; **298:** 2644–53.
7. Riker RR, *et al.* SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301:** 489–99.
8. Gerlach AT, *et al.* An updated focused review of dexmedetomidine in adults. *Ann Pharmacother* 2009; **43:** 2064–74.
9. Farag E. Dexmedetomidine in the neurointensive care unit. *Discov Med* 2010; **9:** 42–5.

Adverse Effects and Precautions

The most common adverse effect of dexmedetomidine is hypotension. Other common adverse effects include hypertension, nausea and vomiting, bradycardia, tachycardia, fever, hypoxia, and anaemia. Patients should be continuously monitored during use. Dexmedetomidine should be used with caution in patients with advanced heart block, or hepatic impairment, or in the elderly.

Interactions

The effects of other CNS depressants may be enhanced by dexmedetomidine. Dexmedetomidine may also increase the effects of other vasodilators or drugs such as cardiac glycosides, that have negative chronotropic effects.

Pharmacokinetics

Dexmedetomidine is about 94% protein bound, but this has been reported to be significantly decreased in patients with hepatic impairment. Dexmedetomidine is almost completely metabolised by direct glucuronidation or by cytochrome P450 isoenzymes. It is excreted mainly as metabolites in the urine and faeces. The terminal elimination half-life is about 2 hours.

References.

1. De Wolf AM, *et al.* The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001; **93:** 1205–9.
2. Anttila M, *et al.* Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 691–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Precedex; *Austral.*: Precedex; *Braz.*: Precedex; *Canad.*: Precedex; *Cz.*: Precedex†; *Denm.*: Dexdor; *Hong Kong*: Precedex; *Indon.*: Precedex; *Irl.*: Dexdor; *Jpn*: Precedex; *Malaysia*: Precedex; *Mex.*: Precedex†; *Norw.*: Dexdor; *NZ*: Precedex; *Philipp.*: Precedex; *Pol.*: Precedex†; *S. Afr.*: Precedex; *Singapore*: Precedex; *Spain*: Dexdor; *Swed.*: Dexdor; *Switz.*: Dexdor; *Thai.*: Precedex; *Turk.*: Precedex†; *UK*: Dexdor; *Ukr.*: Dexdor (Дексдор); *USA*: Precedex.

Diazepam *(BAN, USAN, rINN)*

Diatsepaarni; Diazepám; Diazépam; Diazepamas; Diazepamum; LA-III; NSC-77518; Ro-5-2807; Wy-3467; Диазепам.

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{16}H_{13}ClN_2O$=284.7

CAS — 439-14-5.
ATC — N05BA01.
ATC Vet — QN05BA01.
UNII — Q3JTX2Q7TU.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of diazepam:

Benzo; Black pearl; Blue; Blue bombers; Blue boys; Blue magoo's; Blue thunder; Blues; Drunk pills; La Roche; Ludes; Mother's little helper; Mother's little helpers; Pami; Roaches; Roachies; Roche; V; V's blues; Valleys; Vallies; Vals.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Diazepam). A white or almost white, crystalline powder. Very slightly soluble in water; soluble in alcohol. Protect from light.

USP 36: (Diazepam). An off-white to yellow, practically odourless, crystalline powder. Soluble 1 in 333 of water, 1 in 16 of alcohol, 1 in 2 of chloroform, and 1 in 39 of ether. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between diazepam and several other drugs. Licensed product information for diazepam injection advises against its admixture with other drugs.

Sorption. Substantial adsorption of diazepam onto some plastics may cause problems when giving the drug by continuous intravenous infusion. More than 50% of diazepam in solution may be adsorbed onto the walls of PVC infusion bags and their use should, therefore, be avoided. Giving sets should contain the minimum amount of PVC tubing and should not contain a cellulose propionate volume-control chamber. Suitable materials for infusion containers, syringes, and giving sets for diazepam include glass, polyolefin, polypropylene, and polyethylene.

References.

1. Cloyd JC, *et al.* Availability of diazepam from plastic containers. *Am J Hosp Pharm* 1980; **37:** 492–6.
2. Parker WA, MacCara ME. Compatibility of diazepam with intravenous fluid containers and administration sets. *Am J Hosp Pharm* 1980; **37:** 496–500.
3. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
4. Kowaluk EA, *et al.* Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am J Hosp Pharm* 1983; **40:** 417–23.
5. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Stability. Care should be observed when diluting diazepam injections for infusion because of problems of precipitation. Directions in the licensed product information should be followed regarding diluent and concentration of diazepam and all solutions should be freshly prepared.

Uses and Administration

Diazepam is a long-acting benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnestic properties. Its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. Diazepam is used in the short-term treatment of severe anxiety disorders (p. 1028.1), as a hypnotic in the short-term management of insomnia (p. 1033.2), as a sedative (p. 1032.2) and premedicant (see Anaesthesia, p. 1899.1), as an anticonvulsant (particularly in the management of status epilepticus and febrile convulsions), in the control of muscle spasm of various aetiologies, and in the management of withdrawal symptoms (see also the references on p. 1064.3 and p. 1065.1).

Diazepam is **administered** orally, rectally, and parenterally with the risk of dependence very much influencing the dose and duration of treatment. Doses should be the lowest that can control symptoms and courses of treatment should be short, not normally exceeding 4 weeks, with diazepam being withdrawn gradually (see under Dependence and Withdrawal, p. 1065.1). Elderly and debilitated patients should be given not more than one-half the usual adult dose. Dosage reduction may also be required in patients with hepatic or renal impairment.

Oral use is appropriate for many indications and modified-release formulations are available in some countries. *Rectal* use may be by rectal solution or gel; it has been given as a suppository. Diazepam is also given by deep intramuscular or slow intravenous injection, although absorption after *intramuscular injection* may be erratic and provides lower blood concentrations than those after oral doses. The intramuscular route is usually only used when oral or intravenous dosage is not possible. *Intravenous injection* should be carried out slowly into a large vein of the antecubital fossa at a recommended rate of no more than 1 mL of a 0.5% solution (5 mg) per minute. It is advisable to keep the patient in the supine position and under medical supervision for at least an hour after the dose. Diazepam may be given by continuous *intravenous infusion*; because of the risk of precipitation of diazepam, solutions should be freshly prepared following directions regarding diluent and concentration of diazepam as stated in the licensed product information. Diazepam is substantially adsorbed onto some plastics (see Sorption, above). Facilities for resuscitation should always be available when diazepam is given intravenously.

Diazepam may be given for **severe anxiety** in usual *oral* doses of 2 mg three times daily to a maximum of 30 mg daily; a wider dose range of 4 to 40 mg daily in divided doses is licensed in the USA. Diazepam may be given as a *rectal solution* in a dose of 500 micrograms/kg repeated after 12 hours if necessary. Diazepam may sometimes have to be given by *intramuscular* or *intravenous injection* when a dose of up to 10 mg may be used, repeated if necessary after 4 hours. The *BNF* states that this dose has also been given intravenously for the control of acute panic attacks but should only be used when other measures have failed.

The benzodiazepines have a limited role in **insomnia** and diazepam is used for the short-term management of insomnia associated with anxiety. The *BNF* recommends an *oral* dose of 5 to 15 mg at bedtime, although doses of up to 30 mg are licensed.

Diazepam may be given for **premedication** before general anaesthesia or for **sedation** during minor surgical or investigative procedures. *Oral* doses for premedication are in the range of 5 to 20 mg. When given by *intravenous injection* for premedication or sedation the dose is usually 100 to 200 micrograms/kg or 10 to 20 mg. Diazepam 500 micrograms/kg may also be given as a *rectal* solution.

Diazepam is used in a variety of **seizures**. It is given *orally* as an adjunct in some types of epilepsy; for this purpose, 2 to 60 mg may be given daily in divided doses. A *rectal gel* formulation is also available for adjunctive use in the management of episodes of increased seizure activity in patients with refractory epilepsy; a usual dose of 200 micrograms/kg may be given, and repeated after 4 to 12 hours if necessary. No more than 5 episodes a month and no more than 1 episode every 5 days should be treated with this formulation. For febrile convulsions, status epilepticus, and convulsions due to poisoning, giving a *rectal solution* may be appropriate. Licensed doses for the rectal solution differ but a typical dose is 500 micrograms/kg (maximum of 30 mg); the *BNF* suggests doses of 10 to 20 mg. If convulsions are not controlled by the first dose the use of other anticonvulsive measures is recommended in the licensed product information, however, the *BNF* suggests that the dose may be repeated once after 10 to 15 minutes if seizures are not controlled. Alternatively, diazepam may be given by *intravenous* injection in a dose of 150 to 250 micrograms/kg, repeated after 30 to 60 minutes (the *BNF* suggests a dose of 10 mg which may be repeated once after 10 minutes) if necessary. Other schedules involve giving smaller amounts more frequently or giving diazepam

intramuscularly, though again absorption may be too slow. Once the seizures have been controlled, a slow intravenous infusion providing up to 3 mg/kg over 24 hours has been used to protect against recurrence.

Diazepam 2 to 15 mg daily may be given *orally* in divided doses to alleviate **muscle spasm**. The dose may be increased in severe spastic disorders, such as cerebral palsy, to up to 60 mg daily. If given by intramuscular or slow intravenous *injection* the dose is 10 mg repeated if necessary after 4 hours. When used to control acute drug-induced dystonic reactions, the *BNF* suggests a dose of 5 to 10 mg by *intravenous* injection, repeated as necessary after a minimum of 10 minutes. Larger doses are used in tetanus with 100 to 300 micrograms/kg being given every 1 to 4 hours by intravenous injection. Alternatively 3 to 10 mg/kg may be given over 24 hours by continuous intravenous infusion or by nasoduodenal tube using a suitable liquid oral dose form. Diazepam may also be given as a *rectal solution* in a dose of 500 micrograms/kg, repeated every 12 hours if necessary.

For details of doses in children, see below.

Symptoms of the **alcohol withdrawal syndrome** may be controlled by diazepam given *orally* in a dose of 5 to 20 mg, repeated if necessary after 2 to 4 hours; another approach is to give 10 mg three or four times on the first day reducing to 5 mg three or four times daily as required. Diazepam may need to be given by *injection* if the symptoms are severe and if delirium tremens has developed; 10 to 20 mg by intramuscular or intravenous injection, repeated after 4 hours if necessary, may be adequate, although some patients may require higher doses.

Reviews.
1. Ashton H. Guidelines for the rational use of benzodiazepines: when and what to use. *Drugs* 1994; **48**: 25–40.
2. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry* 2004; **65** (suppl 5): 7–12.
3. Stevens JC, Pollack MH. Benzodiazepines in clinical practice: consideration of their long-term use and alternative agents. *J Clin Psychiatry* 2005; **66** (suppl 2): 21–7.
4. Witek MW, *et al.* Review of benzodiazepine use in children and adolescents. *Psychiatr Q* 2005; **76**: 283–96.
5. Cloos JM, Ferreira V. Current use of benzodiazepines in anxiety disorders. *Curr Opin Psychiatry* 2009; **22**: 90–5.

Administration in children. Diazepam has been given for **premedication** before general anaesthesia or for **sedation** during minor surgical or investigative procedures in children. UK licensed product information suggests the following doses:

orally
- 2 to 10 mg

intravenously (preferably as the emulsion preparation; injection formulations containing benzyl alcohol should be avoided in neonates, see p. 1067.2)
- 100 to 200 micrograms/kg

rectally (as a rectal solution in children aged 1 year and older)
- 250 to 500 micrograms/kg (usually, for practical reasons, a dose of 5 or 10 mg)

The *BNFC* considers that perioperative use of diazepam is not recommended in children as onset and magnitude of response are unreliable, and paradoxical effects may occur.

Diazepam is used in a variety of **seizures**. In some countries a *rectal gel* formulation is available for adjunctive use in the management of episodes of increased seizure activity in children aged 2 years and older with refractory epilepsy; the following doses, repeated once after 4 to 12 hours if necessary, may be given according to age:
- 2 to 5 years: 500 micrograms/kg
- 6 to 11 years: 300 micrograms/kg
- 12 years and older: 200 micrograms/kg

For febrile convulsions, status epilepticus, and convulsions due to poisoning, giving a *rectal solution* may be appropriate. A dose of 500 micrograms/kg of a rectal solution, repeated every 12 hours if necessary, has been recommended in licensed product information for children aged 1 year and over. Alternatively, the *BNFC* suggests giving the following doses, repeated once after 10 minutes if necessary, according to age:
- neonates: 1.25 to 2.5 mg
- 1 month to 2 years: 5 mg
- 2 to 12 years: 5 to 10 mg
- 12 to 18 years: 10 to 20 mg

Doses by *intravenous* injection, given at a rate of not more than 5 mg/minute and repeated if necessary after 30 to 60 minutes, are within the range of 200 to 300 micrograms/kg; alternatively, 1 mg may be given for each year of age. The *BNFC* suggests giving the following doses over 3 to 5 minutes, repeated once after 10 minutes if necessary:
- neonates to 12 years: 300 to 400 micrograms/kg
- 12 to 18 years: 10 mg

Diazepam 2 to 40 mg daily may be given *orally* in divided doses to alleviate **muscle spasm** of various aetiologies. For muscle spasm in cerebral spasticity or postoperative skeletal muscle spasm, the *BNFC* suggests initial oral doses based on age and given twice daily, as follows:
- 1 to 12 months: 250 micrograms/kg
- 1 to 5 years: 2.5 mg
- 5 to 12 years: 5 mg
- 12 to 18 years: 10 mg (maximum of 40 mg daily)

For life-threatening acute drug-induced dystonic reactions, the *BNFC* suggests giving the following doses based on age by *intravenous* injection over 3 to 5 minutes:
- 1 month to 12 years: 100 micrograms/kg
- 12 to 18 years: 5 to 10 mg

The dose may be repeated as necessary after at least 10 minutes.

For muscle spasm in tetanus, the *BNFC* suggests that children aged from 1 month to 18 years may be given 100 to 300 micrograms/kg every 1 to 4 hours by intravenous injection; alternatively, 3 to 10 mg/kg may be given over 24 hours by continuous intravenous infusion or by nasoduodenal tube using a suitable liquid oral dose form.

Diazepam may also be given as a *rectal* solution in a dose of 500 micrograms/kg to children aged 1 year and older, repeated every 12 hours if necessary.

Administration in hepatic impairment. Oxidative metabolism of diazepam is apparently reduced in patients with hepatic impairment, resulting in a prolonged half-life and reduced clearance.[1-3] A reduction in dosage was generally required in these studies, but no specific advice is given in licensed product information for the UK or USA.

1. Branch RA, *et al.* Intravenous administration of diazepam in patients with chronic liver disease. *Gut* 1976; **17**: 975–83.
2. Klotz U, *et al.* Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. *Clin Pharmacol Ther* 1977; **21**: 430–6.
3. Ochs HR, *et al.* Repeated diazepam dosing in cirrhotic patients: cumulation and sedation. *Clin Pharmacol Ther* 1983; **33**: 471–6.

Administration in renal impairment. Diazepam and its metabolites are excreted in urine, and UK licensed product information suggests that dosage reduction may be required in patients with renal impairment, but gives no specific advice on how to do this.

Cardiac arrhythmias. Although not considered to be an antiarrhythmic, diazepam has been tried with good effect in treating the cardiotoxicity of chloroquine poisoning (see p. 652.3). However, diazepam has been reported to possess both antiarrhythmic and pro-arrhythmic properties, possibly depending on the dose.[1]

1. Kumagai K, *et al.* Antiarrhythmic and proarrhythmic properties of diazepam demonstrated by electrophysiological study in humans. *Clin Cardiol* 1991; **14**: 397–401.

Chloroquine poisoning. For reference to the possible use of diazepam to decrease the cardiotoxic effects of chloroquine, see p. 652.3.

Conversion and dissociative disorders. Conversion and dissociative disorders (formerly known as hysteria) are characterised by physical symptoms that occur in the absence of organic disease.[1] Medication has no part to play in the treatment of these disorders unless they are secondary to conditions such as depression or anxiety disorders requiring treatment in their own right.

There have been suggestions that sedatives such as diazepam or midazolam may be used to confirm the diagnosis of hysterical paralysis.[2,3] The test tends to exacerbate organic disease while psychiatric dysfunction may improve.

1. Kihlstrom JF. Dissociative disorders. *Annu Rev Clin Psychol* 2005; **1**: 227–53.
2. Ellis SJ. Diazepam as a truth drug. *Lancet* 1990; **336**: 752–3.
3. Keating JJ, *et al.* Hysterical paralysis. *Lancet* 1990; **336**: 1506–7.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders, and the value of benzodiazepines, see p. 1030.2. Benzodiazepines may also be useful in palliative care for the relief of terminal restlessness and confusion; however, benzodiazepine use alone has been associated with an exacerbation of symptoms. Those that have been tried include diazepam, clonazepam, lorazepam, and midazolam. Parenteral midazolam, given with the antipsychotic haloperidol, is often the treatment of choice in an imminently dying patient with delirium.

Dyspnoea. Despite the hazards of use in patients with any form of respiratory depression or pulmonary insufficiency (see Respiratory System Disorders under Precautions, p. 1068.1) benzodiazepines such as diazepam have been tried in the treatment of dyspnoea (p. 108.3), in the belief that reduction of an elevated respiratory drive may alleviate respiratory distress. However, benefits have not been confirmed. Benzodiazepines may be of use in patients with advanced cancer who have rapid shallow respiration. Some[1] recommend trying a low dose of a benzodiazepine, given either regularly or as required, in palliative care only if anxiety appears to be a major component or trigger of breathlessness and is not relieved by non-pharmacological measures. The *BNF* suggests that 5 to 10 mg daily of diazepam may be helpful.

1. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.

Eclampsia and pre-eclampsia. Diazepam has been used for the initial control of impending or actual eclampsia (p. 511.1), but magnesium sulfate is now generally the preferred treatment.

Epilepsy and other convulsive disorders. Some benzodiazepines such as diazepam are used for the control of status epilepticus (p. 510.2), including status epilepticus in patients with porphyria (but see also Porphyria under Precautions, p. 1067.3), and for febrile convulsions (p. 511.2) and seizures associated with alcohol withdrawal (p. 1735.1); diazepam has also been used in eclampsia (see above) and for neonatal seizures (p. 511.3). Benzodiazepines such as clobazam and clonazepam may be used in the management of epilepsy (p. 506.1), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Diazepam has been used as an adjunct in the management of some types of epilepsy including myoclonus.

References.
1. Rosman NP, *et al.* A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993; **329**: 79–84.
2. Somerville ER, Antony JH. Position statement on the use of rectal diazepam in epilepsy. *Med J Aust* 1995; **163**: 268–9.
3. Uhari M, *et al.* Effect of acetaminophen and low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126**: 991–5.
4. Akinbi MS, Welty TE. Benzodiazepines in the home treatment of acute seizures. *Ann Pharmacother* 1999; **33**: 99–102.
5. Rey E, *et al.* Pharmacokinetic optimisation of benzodiazepine therapy for acute seizures: focus on delivery routes. *Clin Pharmacokinet* 1999; **36**: 409–24.
6. Ogutu BR, *et al.* Pharmacokinetics and anticonvulsant effects of diazepam in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol* 2002; **53**: 49–57.
7. Riss J, *et al.* Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurol Scand* 2008; **118**: 69–86.
8. Anderson M. Benzodiazepines for prolonged seizures. *Arch Dis Child Educ Pract Ed* 2010; **95**: 183–9.

Extrapyramidal disorders. For reference to the use of benzodiazepines in the treatment of antipsychotic-induced extrapyramidal disorders, see Chlorpromazine, p. 1049.2.

Irritable bowel syndrome. Although some benzodiazepines have been used in the management of irritable bowel syndrome (p. 1813.3) there is no evidence to support their use in this condition. The related compound dextofisopam (see Tofisopam, p. 1112.2) is under investigation.

Mania. Benzodiazepines have been used as short-term adjuncts in the initial control of manic episodes in patients with bipolar disorder (p. 397.2) until lithium has achieved its full effect.

Muscle spasm. Diazepam and other benzodiazepines may be used for the relief of muscle spasm (p. 2014.1) of various aetiologies including that secondary to muscle or joint inflammation or trauma, such as in acute **low back pain** (p. 9.2), or resulting from **spasticity** (p. 2014.2), **dystonias** (p. 903.3), **stiff-man syndrome** (see below), **cerebral palsy**, **poisoning**, or **tetanus** (p. 2029.2). High doses are often required and treatment may be limited by adverse effects or by risk of dependence.

STIFF-MAN SYNDROME. Stiff-man syndrome is a rare condition characterised by painful intermittent spasms and rigidity of the axial and limb muscles. Its exact cause is unknown but there is some evidence to implicate autoantibodies against one of the enzymes involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). It is frequently associated with auto-immune diseases and type 1 diabetes mellitus. Patients typically respond to benzodiazepines and this may be of use in the differential diagnosis of the syndrome. Diazepam has been the mainstay of treatment but clonazepam may also be of use, especially in familial startle disease, a rare congenital form of stiff-man syndrome. Although rigidity and spasms in stiff-man syndrome are not completely resolved by diazepam the degree of improvement can be sufficient to restore the functional level to near normal. However, large doses are often required and sedation might be a limiting factor in some patients. Other drugs that have been used when diazepam is ineffective or poorly tolerated include baclofen or sodium valproate but benefit may be less evident. There have been isolated anecdotal reports of improvement with vigabatrin, tiagabine, gabapentin, and levetiracetam; botulinum A toxin has also been tried. Antiepileptics or baclofen may sometimes be combined with benzodiazepines. Corticosteroids may be of benefit, although any response may take several weeks, and the chronic nature of the disorder and the high incidence of

type 1 diabetes mellitus may make their use problematic. Other attempts at immunomodulation such as plasmapheresis have yielded variable results; there is some evidence of the efficacy of immunoglobulins but repeated infusions are required to maintain response.

References.

1. Stayer C, Meinck H-M. Stiff-man syndrome: an overview. *Neurologia* 1998; 13: 83–8.
2. Levy LM, *et al.* The stiff-person syndrome - an autoimmune disorder affecting neurotransmission of γ-aminobutyric acid. *Ann Intern Med* 1999; 131: 522–30.
3. Meinck H-M. Stiff man syndrome. *CNS Drugs* 2001; 15: 515–26.
4. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; 345: 1870–6.
5. Vasconcelos OM, Dalakas MC. Stiff-person syndrome. *Curr Treat Options Neurol* 2003; 5: 79–90.
6. Murinson BB. Stiff-person syndrome. *Neurologist* 2004; 10: 131–7.
7. Dalakas MC. Advances in the pathogenesis and treatment of patients with stiff person syndrome. *Curr Neurol Neurosci Rep* 2008; 8: 48–55.

Nausea and vomiting. Benzodiazepines, particularly lorazepam, are used as adjuncts in the management of nausea and vomiting (p. 1814.3) induced by cancer chemotherapy, particularly anticipatory emesis. Midazolam has been tried for the prophylaxis of postoperative nausea and vomiting; for references, see p. 1086.3.

Premenstrual syndrome. For mention of the limited role of benzodiazepines in the management of premenstrual syndrome, see p. 2272.3.

Schizophrenia. Benzodiazepines may be useful adjuncts to antipsychotics in the initial management of schizophrenia (p. 1031.3).

Sleep-associated movement disorders. Sleep-associated movement disorders (p. 1034.2) rarely require treatment other than the symptomatic treatment of sleep-related medical problems. Some of these conditions, including restless legs syndrome, sleepwalking, and night terrors, have been reported to respond to benzodiazepines. Although the muscle relaxant and anxiolytic action of a benzodiazepine can be helpful in bruxism (teeth grinding) it has been recommended that they should only be prescribed on a short-term basis during the acute phase.

References.

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; 100: 333–7.

Substance dependence. The benzodiazepines are used in the symptomatic management of *alcohol* withdrawal (p. 1735.1), of *opioid* withdrawal (p. 109.2), and of *cocaine* withdrawal (p. 1990.1).

Vertigo. Although intravenous diazepam has been used to abort acute attacks of vertigo of peripheral origin (p. 612.3), it can prolong compensation and recovery from vestibular lesions.[1]

1. Rascol O, *et al.* Antivertigo medications and drug-induced vertigo: a pharmacological review. *Drugs* 1995; 50: 777–91.

Dependence and Withdrawal

The development of dependence is common after regular use of benzodiazepines, even in therapeutic doses for short periods. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in those with marked personality disorders. Benzodiazepines should therefore be withdrawn by gradual reduction of the dose after regular use for even a few weeks; the time needed for withdrawal can vary from about 4 weeks to a year or more. The extent to which tolerance occurs has been debated but appears to involve psychomotor performance more often than anxiolytic effects. Drug-seeking behaviour is uncommon with therapeutic doses of benzodiazepines. High doses of diazepam and other benzodiazepines, injected intravenously, have been abused for their euphoriant effects.

Benzodiazepine withdrawal syndrome. Development of dependence to benzodiazepines cannot be predicted but risk factors include high dosage, regular continuous use, the use of benzodiazepines with a short half-life, use in patients with dependent personality characteristics or a history of drug or alcohol dependence, and the development of tolerance. The mechanism of dependence is unclear but may involve reduced gamma-aminobutyric acid (GABA) activity resulting from down-regulation of GABA receptors.

Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension. Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

Symptoms typical of withdrawal have occurred despite continued use of benzodiazepines and have been attributed either to the development of tolerance or, as in the case of very short-acting drugs such as triazolam, to rapid benzodiazepine elimination. Pseudowithdrawal has been reported in patients who believed incorrectly that their dose of benzodiazepine was being reduced. Benzodiazepine withdrawal syndrome can theoretically be distinguished from these reactions and from rebound phenomena (return of original symptoms at greater than pretreatment severity) by the differing **time course.** A withdrawal syndrome is characterised by its onset, by the development of new symptoms, and by a peak in intensity followed by resolution. Onset of withdrawal symptoms depends on the half-life of the drug and its active metabolites. Symptoms can begin within a few hours after withdrawal of a short-acting benzodiazepine, but may not develop for up to 3 weeks after stopping a longer-acting benzodiazepine. Resolution of symptoms may take several days or months. The dependence induced by short- and long-acting benzodiazepines appears to be qualitatively similar although withdrawal symptoms may be more severe with short-acting benzodiazepines. Rebound effects are also more likely with short-acting benzodiazepines. Rebound and withdrawal symptoms develop particularly rapidly with the very short-acting drug triazolam.

With increased awareness of the problems of benzodiazepine dependence, emphasis has been placed on **prevention** by proper use and careful patient selection. For example, the UK CSM has recommended that benzodiazepines should be reserved for the short-term relief (2 to 4 weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress and is occurring alone or with insomnia or short-term psychosomatic, organic, or psychotic illness.

Withdrawal from long-term benzodiazepine use should generally be encouraged. Established dependence can be difficult to treat; the patient should have professional and family support and behavioural therapy may be helpful. Withdrawal in a specialist centre may be required for some patients. Abrupt withdrawal of benzodiazepines has resulted in severe withdrawal symptoms, so benzodiazepine withdrawal should be flexible and carried out at a tolerable reduction rate that is dependent on the initial dose, duration of use, and clinical response. Short-term users (2 to 4 weeks only) can usually taper off within 2 to 4 weeks; however, long-term users should be withdrawn over several months or more. Clinicians often favour transferring long-term benzodiazepine users stepwise, one dose at a time over about a week, to an equivalent dose of diazepam given at night; the following rough dosage equivalents to *diazepam 5 mg* have been recommended in the UK:

- alprazolam 250 micrograms
- chlordiazepoxide 12.5 mg
- clobazam 10 mg
- clonazepam 250 micrograms
- flurazepam 7.5 to 15 mg
- loprazolam 0.5 to 1 mg
- lorazepam 500 micrograms
- lormetazepam 0.5 to 1 mg
- nitrazepam 5 mg
- oxazepam 10 mg
- temazepam 10 mg

The daily dosage of diazepam can then be reduced in steps of 1 to 2 mg every 2 to 4 weeks. In patients taking high doses of benzodiazepines, it may be appropriate initially to reduce in steps of up to one-tenth of the daily dose every 1 to 2 weeks. If troublesome abstinence effects occur the dose should be held level for a longer period before further reduction; increased dosage should be avoided if possible. Smaller steps of 500 micrograms may be appropriate towards the end of withdrawal. For long-term patients, the time required for complete withdrawal can vary from several months to a year or longer. In many cases the rate of withdrawal is best decided by the patient. Adjuvant therapy with beta blockers, antidepressants, and antipsychotic drugs should be avoided where possible.

Symptoms gradually improve after withdrawal but postwithdrawal syndromes lasting for several weeks or months have been described. Withdrawal symptoms in long-term users usually resolve within 6 to 18 months of the last dose. Continued support may be required for the first year after withdrawal to prevent relapse.

References.

1. CSM. Benzodiazepines, dependence and withdrawal symptoms. *Current Problems 21* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
2. Marriott S, Tyrer P. Benzodiazepine dependence: avoidance and withdrawal. *Drug Safety* 1993; 9: 93–103.
3. Pétursson H. The benzodiazepine withdrawal syndrome. *Addiction* 1994; 89: 1455–59.
4. Ashton H. The treatment of benzodiazepine dependence. *Addiction* 1994; 89: 1535–41.
5. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry* 2005; 66 (suppl 2): 28–33.
6. Denis C, *et al.* Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).
7. Oude Voshaar RC, *et al.* Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry* 2006; 189: 213–20.
8. DoH (England) and the devolved administrations (2007). *Drug misuse and dependence: UK guidelines on clinical management* (updated September 2007). London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive. Also available at: http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf (accessed 26/07/10)
9. Lader M, *et al.* Withdrawing benzodiazepines in primary care. *CNS Drugs* 2009; 23: 19–34.

Adverse Effects

Drowsiness, sedation, muscle weakness, and ataxia are the most frequent adverse effects of diazepam use. They generally decrease on continued dosage and are a consequence of CNS depression. Less frequent effects include vertigo, headache, confusion, depression (but see Effects on Mental Function, p. 1066.1), slurred speech or dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may have a paradoxical excitation which may lead to hostility, aggression, and disinhibition. Jaundice, blood disorders, and hypersensitivity reactions have been reported rarely; raised liver enzyme values have occurred. Respiratory depression and hypotension occasionally occur with high dosage and parenteral use.

Pain and thrombophlebitis may occur with some intravenous formulations of diazepam.

Overdosage can produce CNS depression and coma or paradoxical excitation. However, fatalities are rare when taken alone.

Use of diazepam in the first trimester of pregnancy has occasionally been associated with congenital malformations in the infant but no clear relationship has been established. This topic is reviewed under Pregnancy p. 1067.3. Use of diazepam in late pregnancy has been associated with intoxication of the neonate.

Carcinogenicity. The International Agency for Research on Cancer concluded[1] that there was sufficient evidence from human studies that diazepam did not produce breast cancer, and that there were inadequate data to support its potential carcinogenicity at other sites. For most other benzodiazepines the lack of human studies meant that the carcinogenic risk to humans was not classifiable. However, there appeared to be sufficient evidence of carcinogenicity in *animal* studies for oxazepam to be classified as possibly carcinogenic in humans.

1. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 66* 1996. Also available at: http://monographs.iarc.fr/ENG/Monographs/vol66/volume66.pdf (accessed 15/05/06)

Effects on body temperature. Studies in healthy subjects[1,2] indicate that benzodiazepines can reduce body temperature. After a single oral dose of diazepam 10 mg in 11 subjects, body temperature on exposure to cold fell to a mean of 36.93 degrees compared with 37.08 degrees on exposure without the drug.[1] An 86-year-old woman developed hypothermia[3] after being given nitrazepam 5 mg. After recovery she was mistakenly given another 5-mg dose of nitrazepam and again developed hypothermia. Midazolam (given as anaesthetic premedication) also produces modest decreases in core body temperature, which can be abolished by atropine,[4] but its effects are negligible compared with other elements of the anaesthetic regimen.[5]

Hypothermia has been reported in the neonates of mothers given benzodiazepines during the late stages of pregnancy.

1. Martin SM. The effect of diazepam on body temperature change in humans during cold exposure. *J Clin Pharmacol* 1985; 25: 611–13.
2. Matsukawa T, *et al.* I.M. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. *Br J Anaesth* 1997; 78: 396–9.
3. Impallomeni M, Ezzat R. Hypothermia associated with nitrazepam administration. *BMJ* 1976; 1: 223–4.
4. Matsukawa T, *et al.* Atropine prevents midazolam-induced core hypothermia in elderly patients. *J Clin Anesth* 2001; 13: 504–8.
5. Kurz A, *et al.* Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; 81: 393–8.

Effects on endocrine function. Galactorrhoea with normal serum-prolactin concentrations has been noted in 4 women taking benzodiazepines.[1] Gynaecomastia has been reported in men taking diazepam;[2-4] doses ranged from up to 30 mg daily to up to 140 mg daily. Serum-oestradiol concentrations were raised in some patients. However, raised plasma-testosterone concentrations have also

occurred in men taking diazepam 10 to 20 mg daily for 2 weeks.[5]

1. Kleinberg DL, *et al.* Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977; 296: 589–600.
2. Moerck HJ, Magelund G. Gynaecomastia and diazepam abuse. *Lancet* 1979; i: 1344–5.
3. Bergman D, *et al.* Increased oestradiol in diazepam related gynaecomastia. *Lancet* 1981; ii: 1225–6.
4. Jelenkovic AV, Macukanovic-Golubovic LD. Diazepam-associated gynecomastia. *Ann Pharmacother* 2005; 39: 201.
5. Argüelles AE, Rosner J. Diazepam and plasma-testosterone levels. *Lancet* 1975; ii: 607.

Effects on the eyes. Brown opacification of the lens occurred in 2 patients who took oral diazepam 5 mg or more daily over several years.[1] Severe visual field loss associated with very high doses (100 mg) of diazepam has also been described.[2]

1. Pau H. Braune scheibenförmige Einlagerungen in die Linse nach Langzeitgabe von Diazepam (Valium). *Klin Monatsbl Augenheilkd* 1985; 187: 219–20.
2. Elder MJ. Diazepam and its effects on visual fields. *Aust N Z J Ophthalmol* 1992; 20: 267–70.

Effects on the liver. Cholestatic jaundice[1] and focal hepatic necrosis with intracellular cholestasis[2] have been associated with the use of diazepam.

1. Jick H, *et al.* Drug-induced liver disease. *J Clin Pharmacol* 1981; 21: 359–64.
2. Tedesco FJ, Mills LR. Diazepam (Valium) hepatitis. *Dig Dis Sci* 1982; 27: 470–2.

Effects on mental function. The effects of benzodiazepines on psychomotor performance in laboratory tests[1] are not easily extrapolated to the clinical situation. For example postoperative cognitive dysfunction in the elderly does not seem to be related to benzodiazepine concentration in the blood.[2]

A meta-analysis[3] of 13 studies found that long-term benzodiazepine use is associated with cognitive dysfunction such as impairments in visual-spatial ability, concentration and attention, motor skills, verbal and non-verbal memory, reaction time, and general intellectual ability. A further meta-analysis[4] using some of the above studies suggested that although cognitive function improved after benzodiazepine withdrawal, there remains significant impairment, at least for the first 6 months, when compared with control subjects or normative data and that some impairment may be permanent.

Paradoxical reactions characterised by increased talkativeness, excitement, insomnia, excessive movement, hostility, and rage have been reported[5] with benzodiazepines. These reactions occur in less than 1% of patients and there is some evidence that young or advanced age, genetic predisposition, alcoholism, and psychiatric or personality disorders are risk factors.

Sexual fantasies have been reported in women sedated with intravenous diazepam or midazolam.[6] These appear to be dose-related.[7]

The view that benzodiazepines can cause depression, albeit infrequently, has been queried.[8]

Some benzodiazepines such as clorazepate, are used as antiepileptics. For a review of the effects of antiepileptic therapy on cognition and mood and, in particular, the increased risk of suicidal ideation or behaviour, see p. 508.3.

Adverse effects of alprazolam on behaviour have also been reviewed.[9]

1. Woods JH, *et al.* Abuse liability of benzodiazepines. *Pharmacol Rev* 1987; 39: 251–413.
2. Rasmussen LS, *et al.* Benzodiazepines and postoperative cognitive dysfunction in the elderly. *Br J Anaesth* 1999; 83: 585–9.
3. Barker MJ, *et al.* Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs* 2004; 18: 37–48.
4. Barker MJ, *et al.* Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Arch Clin Neuropsychol* 2004; 19: 437–54.
5. Mancuso CE, *et al.* Paradoxical reactions to benzodiazepines: literature review and treatment options. *Pharmacotherapy* 2004; 24: 1177–85.
6. Dundee JW. Fantasies during sedation with intravenous midazolam or diazepam. *Med Leg J* 1990; 58: 29–34.
7. Brahams D. Benzodiazepine sedation and allegations of sexual assault. *Lancet* 1989; i: 1339–40.
8. Patten SB, Love EJ. Drug-induced depression: incidence, avoidance and management. *Drug Safety* 1994; 10: 203–19.
9. Cole JO, Kando JC. Adverse behavioral events reported in patients taking alprazolam and other benzodiazepines. *J Clin Psychiatry* 1993; 54 (suppl): 49–61.

Effects on the nervous system. There are a few isolated reports of extrapyramidal symptoms in patients taking benzodiazepines.[1-4] Benzodiazepines have been used to treat such symptoms induced by antipsychotics (see Extrapyramidal Disorders under Chlorpromazine, p. 1049.2).

1. Rosenbaum AH, De La Fuente JR. Benzodiazepines and tardive dyskinesia. *Lancet* 1979; ii: 900.
2. Sandyk R. Orofacial dyskinesias associated with lorazepam therapy. *Clin Pharm* 1986; 5: 419–21.
3. Stolarek IH, Ford MJ. Acute dystonia induced by midazolam and abolished by flumazenil. *BMJ* 1990; 300: 614.
4. Joseph AB, Wroblewski BA. Paradoxical akathisia caused by clonazepam, clorazepate and lorazepam in patients with traumatic encephalopathy and seizure disorders: a subtype of benzodiazepine-induced disinhibition? *Behav Neurol* 1993; 6: 221–3.

ENCEPHALOPATHY. Prolonged use of midazolam with fentanyl has been associated with encephalopathy in infants sedated under intensive care.[1]

1. Bergman I, *et al.* Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr* 1991; 119: 644–9.

Effects on sexual function. The sedative effects of benzodiazepines may reduce sexual arousal and lead to impotence in some patients. Conversely sexual performance may be improved by therapy if it was previously impaired by anxiety.

Increased libido and orgasmic function has been reported in 2 women after withdrawal of long-term benzodiazepine use.[1]

1. Nutt D, *et al.* Increased sexual function in benzodiazepine withdrawal. *Lancet* 1986; ii: 1101–2.

Effects on skeletal muscle. In a report[1] of 2 patients who developed rhabdomyolysis secondary to hyponatraemia it was suggested that the use of benzodiazepines might have contributed to the rhabdomyolysis. Of 8 reported cases of rhabdomyolysis associated with hyponatraemia, 5 had received benzodiazepines. Rhabdomyolysis associated with intravenous drug abuse of oral temazepam formulations has also been reported.[2]

1. Fernández-Real JM, *et al.* Hyponatremia and benzodiazepines result in rhabdomyolysis. *Ann Pharmacother* 1994; 28: 1200–1.
2. Deighan CJ, *et al.* Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. *Q J Med* 2000; 93: 29–33.

Effects on the skin. There have been rare reports of cutaneous reactions to benzodiazepines, including contact dermatitis, fixed drug eruptions, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 2 allergic skin reactions attributed to diazepam among 4707 recipients of the drug[1] giving a reaction rate of 0.4 per 1000 recipients.

1. Bigby M, *et al.* Drug-induced cutaneous reactions. *JAMA* 1986; 256: 3358–63.

Hypersensitivity. Hypersensitivity reactions including anaphylaxis are very rare after use of diazepam. Reactions have been attributed to the polyoxyl castor oil (p. 2202.3) vehicle used for some parenteral formulations.[1] There is also a report of a type I hypersensitivity reaction to a lipid emulsion formulation of diazepam.[2]

See also Effects on the Skin, above, and Local Reactions, below.

1. Hüttel MS, *et al.* Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid MR). *Br J Anaesth* 1980; 52: 77–9.
2. Deardon DJ, Bird GLA. Acute (type 1) hypersensitivity to iv Diazemuls. *Br J Anaesth* 1987; 59: 391.

Local reactions. Ischaemia and gangrene have been reported after accidental intra-arterial injection of diazepam.[1,2] Clinical signs may not occur until several days after the event. Pain and thrombophlebitis after intravenous use may be similarly delayed. Local reactions after intravenous injection have been attributed to the vehicle, and have been seen more often when diazepam is given as a solution in propylene glycol than in polyoxyl castor oil.[3] An emulsion of diazepam in soya oil and water has been associated with a lower incidence of local reactions.[3] Pain and phlebitis may also be caused by precipitation of diazepam at the site of infusion.[4] Arterial spasm in a patient given diazepam intravenously was probably due to pressure from a cuff on the arm being inflated causing extravasation of diazepam out of the vein and into the radial artery.[5]

Local irritation has also occurred after rectal use of diazepam.[6]

For a report of the exacerbation of diazepam-induced thrombophlebitis by penicillamine, see p. 1070.3.

1. Gould JDM, Lingam S. Hazards of intra-arterial diazepam. *BMJ* 1977; 2: 298–9.
2. Rees M, Dormandy J. Accidental intra-arterial injection of diazepam. *BMJ* 1980; 281: 289–90.
3. Olesen AS, Hüttel MS. Local reactions to iv diazepam in three different formulations. *Br J Anaesth* 1980; 52: 609–11.
4. Hussey EK, *et al.* Correlation of delayed peak concentration with infusion-site irritation following diazepam administration. *DICP Ann Pharmacother* 1990; 24: 678–80.
5. Tin LNW, *et al.* Arterial spasm after administration of diazepam. *Br J Anaesth* 1994; 72: 139.
6. Hansen BC, *et al.* Local irritation after administration of diazepam in a rectal solution. *Br J Anaesth* 1989; 63: 287–9.

Overdosage. Impairment of consciousness is fairly rapid in poisoning by benzodiazepines.[1] Deep coma or other manifestations of severe depression of brainstem vital functions are rare; more common is a sleep-like state from which the patient can be temporarily roused by appropriate stimuli. There is usually little or no respiratory depression, and cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension. Since tolerance to benzodiazepines develops rapidly, consciousness is often regained while concentrations of drug in the blood are higher than those which induced coma. Anxiety and insomnia can occur during recovery from acute overdosage, while a full-blown withdrawal syndrome, possibly with major convulsions, can occur in patients who have previously been chronic users.

During the years 1980 to 1989, 1576 fatal poisonings in Britain were attributed to benzodiazepines.[2] Of these, 891 were linked to overdosage with benzodiazepines alone and another 591 to overdosage combined with alcohol. A comparison of these mortality statistics with prescribing data for the same period, to calculate a toxicity index of deaths per million prescriptions, suggested that there were differences between the relative toxicities of individual benzodiazepines in overdosage; flurazepam and temazepam were found to be the most toxic in overdosage. A later study of another 303 cases of benzodiazepine poisoning[3] supported these differences in toxicity as well as pointing to the relative safety of the benzodiazepines in overdosage. See also under Alprazolam, p. 1036.1.

1. Ashton CH, *et al.* Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; 8: 1–59.
2. Serfaty M, Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry* 1993; 163: 386–93.
3. Buckley NA, *et al.* Relative toxicity of benzodiazepines in overdose. *BMJ* 1995; 310: 219–21.

Treatment of Adverse Effects

The treatment of benzodiazepine overdosage is generally symptomatic and supportive. Patients who are asymptomatic after 4 hours are unlikely to develop severe toxicity. Activated charcoal may be given orally if the amount ingested was large (see below) and treatment is within one hour of ingestion. The specific benzodiazepine antagonist, flumazenil (p. 1551.3), is rarely required, and can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients (see p. 1552.1); the UK Poisons Information Service, contra-indicates its use in mixed overdoses. However, use of flumazenil may sometimes provide an alternative to ventilation, particularly in patients with severe respiratory disorders, or in children who are naive to benzodiazepines.

For a discussion of the general principles of the management of acute poisoning, see p. 1537.1.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with benzodiazepines to be uncertain. However, it is suggested that oral activated charcoal may be considered in adults and children if this is given within 1 hour of ingestion and the quantity of benzodiazepine exceeds the following amount, provided that the airway can be protected:

- alprazolam: 100 micrograms/kg
- bromazepam: 1 mg/kg
- chlordiazepoxide: 1.5 mg/kg
- clobazam: 1 mg/kg
- clonazepam: 500 micrograms/kg
- diazepam: 500 micrograms/kg
- flunitrazepam: 100 micrograms/kg
- flurazepam: 2 mg/kg
- loprazolam: 100 micrograms/kg
- lorazepam: 100 micrograms/kg
- lormetazepam: 70 micrograms/kg
- midazolam: 1 mg/kg
- nitrazepam: 400 micrograms/kg
- oxazepam: 3 mg/kg
- prazepam: 1 mg/kg
- temazepam: 2 mg/kg
- triazolam: 50 micrograms/kg

Elderly patients or those with severe hepatic disease may require intervention at a lower amount.

Precautions

Diazepam should be avoided in patients with pre-existing CNS depression or coma, respiratory depression, acute pulmonary insufficiency, myasthenia gravis, or sleep apnoea, and used with care in those with chronic pulmonary insufficiency. Diazepam should be given with care to elderly or debilitated patients who may be more prone to adverse effects. Caution is required in patients with muscle weakness, or those with hepatic or renal impairment, who may require reduced doses; its use should be avoided in severe hepatic impairment. The sedative effects of diazepam are most marked during the first few days of use; affected patients should not drive or operate machinery (see also Driving, p. 1067.1). Monitoring of cardiorespiratory function is generally recommended when benzodiazepines are used for deep sedation.

Diazepam is not appropriate for the treatment of chronic psychosis or for phobic or obsessional states. Diazepam-induced disinhibition may precipitate suicide or aggressive behaviour and it should not, therefore, be used alone to treat depression or anxiety associated with depression; it

should also be used with care in patients with personality disorders. Caution is required in patients with organic brain changes particularly arteriosclerosis. In cases of bereavement, psychological adjustment may be inhibited by diazepam.

Licensed product information for diazepam and other benzodiazepines may advise against their use in patients with glaucoma, but the rationale for this contra-indication is unclear.

For warnings on the use of benzodiazepines during pregnancy and breast feeding, see below.

Dependence characterised by a withdrawal syndrome may develop after regular use of diazepam, even in therapeutic doses for short periods (see p. 1065.1); because of the risk of dependence, diazepam should be used with caution in patients with a history of alcohol or drug abuse.

Since hypotension and apnoea may occur when benzodiazepines are given intravenously it has been recommended that this route should only be used when facilities for reversing respiratory depression with mechanical ventilation are available. Patients should remain supine and under medical supervision for at least one hour after intravenous injection. Intravenous infusion is best undertaken in specialist centres with intensive care facilities where close and constant supervision can be undertaken.

Breast feeding. The last available guidance from the American Academy of Pediatrics considered that benzodiazepine use by nursing mothers for long periods was a cause for concern; anxiolytic drugs appear in breast milk and could conceivably alter CNS function in the infant both in the short and long term.[1] Similarly, in the UK the CSM has recommended[2] that benzodiazepines should not be given to breast-feeding mothers. In one reviewer's opinion[3] the limited distribution into breast milk did not constitute a hazard to the breast-fed infant but the infant should be monitored for sedation and the inability to suckle. Another group has also reported a low incidence of toxicity and adverse effects in the breast-fed infants of mothers taking psychotropic drugs including benzodiazepines.[4] It has been suggested[5] that if a benzodiazepine must be used during breast feeding it would be preferable to use a short-acting drug with minimal distribution into breast milk and inactive metabolites; oxazepam, lorazepam, alprazolam, or midazolam might be suitable.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. (Retired May 2010) Correction. *ibid*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. CSM/MCA. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; 23: 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
3. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; 8: 461–75.
4. Birnbaum CS, *et al.* Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Abstract: *Pediatrics* 1999; 104: 104. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e11 (accessed 28/04/04)
5. Chisholm CA, Kuller JA. A guide to the safety of CNS-active agents during breastfeeding. *Drug Safety* 1997; 17: 127–42.

Cardiovascular disorders. See under Respiratory System Disorders, p. 1068.1.

Driving. Patients affected by drowsiness while taking benzodiazepines should not drive or operate machinery. In the UK, it is an offence to drive while unfit due to the influence of any drug, and benzodiazepines are considered to be the most likely psychotropic medication to impair driving performance, particularly the long-acting compounds.[1] However, it is also noted that drivers with psychiatric illnesses may be safer when well controlled with regular medication than when ill. In addition there are restrictions on holding a driving licence for those who persistently misuse or have a dependency on benzodiazepines.

A meta-analysis[2] of 11 epidemiological studies of the effect of benzodiazepines on driving abilities found that patients taking benzodiazepines had a significantly increased risk of motor vehicle collisions when compared with non-users. Older adults were found to have a risk of collision similar to that in mixed-age groups, despite their increased susceptibility to some effects of benzodiazepines such as daytime fatigue and adverse cognitive effects; this paradox may be explained by less frequent or less risky driving patterns of older adults. The meta-analysis also examined 16 experimental studies of benzodiazepine use (in both healthy subjects and in patients) and performance in driving simulators or on-road tests. No delay or slowing of brake reaction time was found although maintaining road position was more difficult with benzodiazepine use.

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)
2. Rapoport MJ, *et al.* Benzodiazepine use and driving: a meta-analysis. *J Clin Psychiatry* 2009; 70: 663–73.

The elderly. Old age may alter the distribution, elimination, and clearance of benzodiazepines.[1,2] Metabolic clearance of benzodiazepines metabolised mainly by oxidation appears to be reduced but not clearance of those biotransformed by glucuronide conjugation or nitroreduction. Prolonged half-life in the elderly may be a result of such a decrease in clearance or of an increase in the volume of distribution. The clinical consequence of these changes depends on factors such as dosage schedule and extent of first-pass extraction by the liver.

Irrespective of pharmacokinetic changes, the elderly may have increased sensitivity to acute doses of benzodiazepines.[1-3] Impairment of memory, cognitive function, and psychomotor performance and behaviour disinhibition may be more common than with younger patients.[4] Long-term use commonly exacerbates underlying dementia in elderly patients.[4]

There is evidence to suggest an increased rate of hip fracture due to falls among elderly patients taking benzodiazepines.[5,6] A review[5] of 11 epidemiological studies suggested that benzodiazepine use in the elderly increased the risk of hip fracture; however, results were equivocal with some hospital-based studies finding no significant increase in risk. More consistent results were seen when such studies were excluded: the risk of fracture was increased by about 50% with benzodiazepine use. There was little evidence to suggest that the risk differed between short- and long-acting benzodiazepines although the correlation between hip fracture and benzodiazepine half-life remains controversial. Patients using higher doses and those who had recently started therapy were found to have the highest risk of hip fracture. A later cohort study[6] suggested that the risk is highest during the first 2 weeks of starting therapy and declines thereafter.

The upshot of the pharmacokinetic and pharmacodynamic changes of benzodiazepines in the elderly is that adverse effects may be more frequent in these patients and lower doses are commonly required. If use of a benzodiazepine is considered necessary in elderly patients, a short-acting drug is to be preferred. It should also be remembered that the elderly are at increased risk of sleep-related breathing disorders, such as sleep apnoea and the use of hypnotics such as benzodiazepines should be avoided in these patients (see Respiratory System Disorders, p. 1068.1).

1. Greenblatt DJ, *et al.* Implications of altered drug disposition in elderly: studies of benzodiazepines. *J Clin Pharmacol* 1989; 29: 866–72.
2. Greenblatt DJ, *et al.* Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly: therapeutic considerations. *Clin Pharmacokinet* 1991; 21: 165–77 and 262–73.
3. Swift CG. Pharmacodynamics: changes in homeostatic mechanisms, receptor and target organ sensitivity in the elderly. *Br Med Bull* 1990; 46: 36–52.
4. Juergens SM. Problems with benzodiazepines in elderly patients. *Mayo Clin Proc* 1993; 68: 818–20.
5. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. *CNS Drugs* 2003; 17: 825–37.
6. Wagner AK, *et al.* Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med* 2004; 164: 1567–72.

Formulation. Parenteral formulations of diazepam may contain the excipient benzyl alcohol, which has been associated with a fatal toxic syndrome in neonates (see p. 1741.1). Licensed product information recommends that such formulations should not be used in premature babies or neonates. Benzyl alcohol poisoning has also been reported with prolonged use of high-dose intravenous infusions of diazepam.[1]

The excipients polyethylene glycol and propylene glycol are included in some benzodiazepine preparations including those of diazepam and lorazepam and toxicity due to these excipients have also been reported (see Toxicity, under Propylene Glycol, p. 2205.3).

1. López-Herce J, *et al.* Benzyl alcohol poisoning following diazepam intravenous infusion. *Ann Pharmacother* 1995; 29: 632.

Hangover effects. Long-acting benzodiazepines accumulate in the body to a greater extent than ones with a shorter half-life. Although this might be expected to increase the frequency of daytime sedation and impairment of performance (so-called hangover effects) after a hypnotic dose, such a straightforward relationship has not always occurred in practice.[1]

Anterograde amnesia is more common with short-acting drugs such as triazolam; 'traveller's amnesia' has been used to describe amnesia in persons taking benzodiazepines for sleep disturbances resulting from jet lag.[2]

1. Greenblatt DJ, *et al.* Neurochemical and pharmacokinetic correlates of the clinical action of benzodiazepine hypnotic drugs. *Am J Med* 1990; 88 (suppl 3A): 18S–24S.
2. Meyboom RHB. Benzodiazepines and pilot error. *BMJ* 1991; 302: 1274–5.

High-altitude disorders. Sleep may be impaired at high altitude due to frequent arousals associated with pronounced oxygen desaturation and periodic breathing. Traditional advice has been that sedatives should not be given at high altitude.[1] Caution may also be warranted at moderate altitudes especially in non-acclimatised climbers.[2] It has been argued that since diazepam, and possibly other sedatives, blunt the hypoxic ventilatory response, sleep hypoxaemia might be exacerbated (see also Respiratory System Disorders, p. 1068.1). A small study[3] has suggested that small doses of a short-acting benzodiazepine, such as 10 mg of temazepam, might actually improve the subjective quality of sleep and reduce episodes of arterial desaturation without changing mean oxygen saturation. Another small study[4] also found that 10-mg doses of temazepam were effective in reducing periodic breathing; daytime performance at altitude was not found to be impaired. However, the possibility of an interaction between acetazolamide taken for prophylaxis or treatment of acute mountain sickness and the benzodiazepine should be borne in mind; ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of triazolam by acetazolamide.[5]

1. Sutton JR, *et al.* Insomnia, sedation, and high altitude cerebral oedema. *Lancet* 1979; i: 165.
2. Röggla G, *et al.* Effect of temazepam on ventilatory response at moderate altitude. *BMJ* 2000; 320: 56.
3. Dubowitz G. Effect of temazepam on oxygen saturation and sleep quality at high altitude: randomised placebo controlled crossover trial. *BMJ* 1998; 316: 587–9.
4. Nickol AH, *et al.* Temazepam at high altitude reduces periodic breathing without impairing next-day performance: a randomized cross-over double-blind study. *J Sleep Res* 2006; 15: 445–54.
5. Masuyama S, *et al.* Ondine's curse': side effect of acetazolamide? *Am J Med* 1989; 86: 637.

Neonates. A retrospective review of records from 63 infants given lorazepam or midazolam in a neonatal intensive-care unit indicated that there were 14 cases of adverse effects associated with benzodiazepine use (seizures in 6 cases, hypotension in 5, and respiratory depression in 3).[1] Seven of these were associated with intravenous bolus doses of lorazepam and the remainder with continuous midazolam infusions. Despite the limitations of the study, the incidence of adverse effects in this group seemed high, and the authors recommended that benzodiazepine use in neonates be accompanied by close monitoring. See also Formulation, above.

1. Ng E, *et al.* Safety of benzodiazepines in newborns. *Ann Pharmacother* 2002; 36: 1150–5.

Nervous system disorders. Benzodiazepines can reduce cerebral perfusion pressure and blood oxygenation to an extent that results in irreversible neurological damage in patients with head injuries. Consequently, they should be given with great care to such patients.[1,2] Their use should be avoided for the control of seizures in patients with head injuries or other acute neurological lesions as these patients can be managed effectively with phenytoin.

1. Eldridge PR, Punt JAG. Risks associated with giving benzodiazepines to patients with acute neurological injuries. *BMJ* 1990; 300: 1189–90.
2. Papazian L, *et al.* Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. *Br J Anaesth* 1993; 71: 267–71.

EPILEPSY. As with other antiepileptic drugs,[1] there have been rare reports of benzodiazepines producing paradoxical exacerbation of seizures in patients with epilepsy.[2-5]

1. Guerrini R, *et al.* Antiepileptic drug-induced worsening of seizures in children. *Epilepsia* 1998; 39 (suppl 3): S2–S10.
2. Prior PF, *et al.* Intravenous diazepam. *Lancet* 1971; 2: 434–5.
3. Tassinari CA, *et al.* A paradoxical effect: status epilepticus induced by benzodiazepines (Valium and Mogadon). *Electroencephalogr Clin Neurophysiol* 1971; 31: 182.
4. Di Mario FJ, Clancy RR. Paradoxical precipitation of tonic seizures by lorazepam in a child with atypical absence seizures. *Pediatr Neurol* 1988; 4: 249–51.
5. Borusiak P, *et al.* Seizure-inducing paradoxical reaction to antiepileptic drugs. *Brain Dev* 2000; 22: 243–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diazepam as probably porphyrinogenic; it should be prescribed only for compelling indications and precautions should be considered in all patients.[1]

Intravenous diazepam has been used successfully, however, to control status epilepticus occurring after the acute porphyric attack.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Pregnancy. Benzodiazepines have been widely used in pregnant patients.[1] Use of benzodiazepines in the *third trimester* and during *labour* seems to be associated in some infants with neonatal withdrawal symptoms or the floppy infant syndrome. Also a small number exposed *in utero* to benzodiazepines have shown slow development in the early years but by 4 years of age most had developed normally, and for those that had not it was not possible to prove a cause-effect relationship with benzodiazepine

exposure. In a meta-analysis[2] of live births after benzodiazepine use during the *first trimester* of pregnancy, pooled data from cohort studies showed no apparent association between benzodiazepine use and the risk of major malformations or oral cleft alone. There was, however, a small but significantly increased risk of oral cleft according to data from case-control studies. Although benzodiazepines did not appear to be a major human teratogen, use of ultrasonography was advised to rule out visible forms of cleft lip. A more recent study[3] of exposure to benzodiazepines and/or the hypnotics zaleplon, zolpidem, and zopiclone during early pregnancy in 1979 infants and during late pregnancy in 401 infants found an increased risk of premature birth and low birth-weight but no significant effect on intra-uterine growth for each group of infants; the risk of premature birth appeared to be higher in the latter group. Although no increased risk of oral cleft was found in exposed infants, there was a tentative association with the occurrence of pyloric stenosis and small intestinal atresia. A study[4] of 112 infants born to women who attempted suicide with large doses of diazepam (range: 25 to 800 mg) did not find an increase in the rate of congenital abnormalities; findings were similar in 10 other pregnant women who took between 60 and 500 mg of medazepam in suicide attempts.[5] Nevertheless, the UK CSM has recommended[6] that women of child-bearing potential prescribed benzodiazepines should be advised to contact the physician about stopping the drug if they intend to become, or suspect that they are, pregnant.

1. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; 8: 461–75.
2. Dolovich LR, *et al.* Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998; 317: 839–43.
3. Wikner BN, *et al.* Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Safety* 2007; 16: 1203–10.
4. Gidai J, *et al.* No association found between use of very large doses of diazepam by 112 pregnant women for a suicide attempt and congenital abnormalities in their offspring. *Toxicol Ind Health* 2008; 24: 29–39.
5. Gidai J, *et al.* A study of the effects of large doses of medazepam used for self-poisoning in 10 pregnant women on fetal development. *Toxicol Ind Health* 2008; 24: 61–8.
6. CSM/MCA. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; 23: 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232406&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)

Respiratory system disorders. Benzodiazepines may affect the control of ventilation during sleep and may worsen sleep apnoea or other sleep-related breathing disorders especially in patients with chronic obstructive pulmonary disease or cardiac failure.[1] Risk factors for sleep apnoea, which often goes undiagnosed, include old age, obesity, male gender, postmenopausal status in women, and a history of heavy snoring. Although benzodiazepines may reduce sleep fragmentation, their long-term use may result in conversion from partial to complete obstructive sleep apnoea in heavy snorers or in short repetitive central sleep apnoea in patients with recent myocardial infarction.

For concerns about the use of benzodiazepines in patients with sleep hypoxaemia due to high altitude see High-altitude Disorders, p. 1067.3.

1. Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990; 88 (suppl 3A): 25S–28S.

Interactions

Enhanced sedation or respiratory and cardiovascular depression may occur if diazepam or other benzodiazepines are given with other drugs that have CNS-depressant properties; these include alcohol, antidepressants, sedative antihistamines, antipsychotics, general anaesthetics, other hypnotics or sedatives, and opioid analgesics. The metabolism of most benzodiazepines is mediated mainly by the cytochrome P450 system, particularly the isoenzymes CYP2C19 and CYP3A4. Hence, adverse effects may also be produced by use with drugs that inhibit or induce or are metabolised by these isoenzymes. Drugs that have been reported to alter the pharmacokinetics of benzodiazepines are discussed in detail below but few of these interactions are likely to be of clinical significance. Benzodiazepines such as alprazolam, diazepam, and midazolam that are metabolised mainly by hepatic microsomal oxidation may be more susceptible to pharmacokinetic changes than those eliminated mainly by glucuronide conjugation such as lorazepam, oxazepam, and temazepam.

Analgesics. The peak plasma concentration of oxazepam was significantly decreased when *diflunisal* was given to 6 healthy subjects, while the renal clearance of the glucuronide metabolite was reduced and its mean elimination half-life increased from 10 to 13 hours.[1] Diflunisal also displaced oxazepam from plasma protein binding sites *in vitro*. *Aspirin* shortened the time to induce anaesthesia with midazolam in 78 patients also possibly due to competition for plasma protein binding sites.[2] *Paracetamol* produced no significant change in plasma concentrations of diazepam or its major metabolite and only marginal changes in urine concentrations in 4 healthy subjects.[3]

Benzodiazepines such as diazepam, lorazepam, and midazolam may be used with opioid analgesics in anaesthetic or analgesic regimens. An additive sedative effect is to be expected[4] but there are also reports of severe respiratory depression with midazolam and *fentanyl*[5] or sudden hypotension with midazolam and fentanyl[6] or *sufentanil*.[7] The clearance of midazolam appears to be reduced by fentanyl,[8] possibly as a result of competitive inhibition of metabolism by the cytochrome P450 isoenzyme CYP3A. Careful monitoring is therefore required during use of midazolam with these opioids and the dose of both drugs may need to be reduced. Synergistic potentiation of the induction of anaesthesia has been reported between midazolam and fentanyl,[9] but one study has suggested that midazolam can reduce the analgesic effects of sufentanil.[10] Pretreatment with *morphine* or *pethidine* has decreased the rate of oral absorption of diazepam. This has been attributed to the effect of opioid analgesics on gastrointestinal motility.[11]

Dextropropoxyphene prolonged the half-life and reduced the clearance of alprazolam but not diazepam or lorazepam in healthy subjects.[12]

Hallucinations have been reported[13] after oral sedation with triazolam in a patient suspected of taking large quantities of *oxycodone* tablets.

1. Van Hecken AM, *et al.* The influence of diflunisal on the pharmacokinetics of oxazepam. *Br J Clin Pharmacol* 1985; 20: 225–34.
2. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; 3: 247–51.
3. Mulley BA, *et al.* Interactions between diazepam and paracetamol. *J Clin Pharm* 1978; 3: 25–35.
4. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; 68: 282–5.
5. Yaster M, *et al.* Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; 86: 463–7.
6. Burtin P, *et al.* Hypotension with midazolam and fentanyl in the newborn. *Lancet* 1991; 337: 1545–6.
7. West JM, *et al.* Sudden hypotension associated with midazolam and sufentanil. *Anesth Analg* 1987; 66: 693–4.
8. Hase I, *et al.* I.V. fentanyl decreases the clearance of midazolam. *Br J Anaesth* 1997; 79: 740–3.
9. Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth* 1990; 64: 45–7.
10. Luger TJ, Morawetz RF. Clinical evidence for a midazolam-sufentanil interaction in patients with major trauma. *Clin Pharmacol Ther* 1991; 49: 133.
11. Gamble JAS, *et al.* Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; 48: 1181–5.
12. Abernethy DR, *et al.* Interaction of propoxyphene with diazepam, alprazolam and lorazepam. *Br J Clin Pharmacol* 1985; 19: 51–7.
13. Goodchild JH, Donaldson M. Hallucinations and delirium in the dental office following triazolam administration. *Anesth Prog* 2005; 52: 17–20.

Antiarrhythmics. An interaction between clonazepam and existing therapy with *amiodarone* was suspected in a 78-year-old man who had symptoms of benzodiazepine toxicity 2 months after starting with clonazepam 500 micrograms given at bedtime for restless leg syndrome;[1] symptoms resolved on withdrawal of clonazepam.

1. Witt DM, *et al.* Amiodarone-clonazepam interaction. *Ann Pharmacother* 1993; 27: 1463–4.

Antibacterials. Both *erythromycin*[1] and *troleandomycin*[2] have been reported to inhibit the hepatic metabolism of triazolam in healthy subjects. Peak plasma-triazolam concentrations were increased, half-life prolonged, and clearance reduced. Troleandomycin prolonged the psychomotor impairment and amnesia produced by triazolam.[2] Loss of consciousness after erythromycin infusion in a child premedicated with midazolam was attributed to a similar interaction,[3] and increases in peak plasma concentrations of midazolam with profound and prolonged sedation have been reported after use of erythromycin.[4] Use of midazolam with erythromycin should be avoided or the dose of midazolam reduced by 50 to 75%. The clearance of midazolam is also reduced by *clarithromycin*, with an approximate doubling of the benzodiazepine's oral bioavailability.[5,6] Licensed product information for *quinupristin/dalfopristin* states that it too may increase plasma concentrations of midazolam. *Roxithromycin* has been reported[7] to have some effects on the pharmacokinetics and pharmacodynamics of midazolam but these changes were not thought clinically relevant. However, it was recommended that as a precaution the lowest possible effective dose of midazolam should be used when given with roxithromycin. In another study[8] *azithromycin* did not appear to have any effect on the metabolism or psychomotor effects of midazolam.

There is an isolated report of significant rises in steady-state blood-midazolam concentration coinciding with dosage of *ciprofloxacin*.[9] Also ciprofloxacin has been reported to reduce diazepam clearance and prolong its terminal half-life,[10] although psychometric tests did not show any changes in diazepam's pharmacodynamics. Ciprofloxacin appears to have no effect on the pharmacokinetics or pharmacodynamics of temazepam.[11]

Isoniazid has been reported to increase the half-life of a single dose of diazepam[12] and triazolam[13] but not of oxazepam[13] in healthy subjects. In contrast, *rifampicin* has decreased the half-life of alprazolam,[14] diazepam,[15] and nitrazepam[16] and more or less abolishes the effects of midazolam[17] and triazolam,[18] while *ethambutol* has no effect on diazepam pharmacokinetics.[12] In patients receiving therapy for tuberculosis with isoniazid, rifampicin, and ethambutol the half-life of a single diazepam dose was shortened and its clearance increased.[12] Thus the enzyme-inducing effect of rifampicin appears to predominate over the enzyme-inhibiting effect of isoniazid.

1. Phillips JP, *et al.* A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol* 1986; 6: 297–9
2. Warot D, *et al.* Troleandomycin-triazolam interaction in healthy volunteers: pharmacokinetic and psychometric evaluation. *Eur J Clin Pharmacol* 1987; 32: 389–93.
3. Hiller A, *et al.* Unconsciousness associated with midazolam and erythromycin. *Br J Anaesth* 1990; 65: 826–8.
4. Olkkola KT, *et al.* A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; 53: 298–305.
5. Gorski JC, *et al.* The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther* 1998; 64: 133–43.
6. Quinney SK, *et al.* Interaction between midazolam and clarithromycin in the elderly. *Br J Clin Pharmacol* 2008; 65: 98–109.
7. Backman JT, *et al.* A pharmacokinetic interaction between roxithromycin and midazolam. *Eur J Clin Pharmacol* 1994; 46: 551–5.
8. Mattila MJ, *et al.* Azithromycin does not alter the effects of oral midazolam on human performance. *Eur J Clin Pharmacol* 1994; 47: 49–52.
9. Orko R, *et al.* Intravenous infusion of midazolam, propofol and vecuronium in a patient with severe tetanus. *Acta Anaesthesiol Scand* 1988; 32: 590–2.
10. Kamali F, *et al.* The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* 1993; 44: 365–7.
11. Kamali F, *et al.* The influence of ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of temazepam in the young and elderly. *J Clin Pharm Ther* 1994; 19: 105–9.
12. Ochs HR, *et al.* Diazepam interaction with antituberculous drugs. *Clin Pharmacol Ther* 1981; 29: 671–8.
13. Ochs HR, *et al.* Differential effect of isoniazid on triazolam oxidation and oxazepam conjugation. *Br J Clin Pharmacol* 1983; 16: 743–6.
14. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP 2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1995; 5: 725–34.
15. Ohnhaus EE, *et al.* The effect of antipyrine and rifampin on the metabolism of diazepam. *Clin Pharmacol Ther* 1987; 42: 148–56.
16. Brockmeyer NH, *et al.* Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; 28: 387–93.
17. Backman JT, *et al.* Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin Pharmacol Ther* 1996; 59: 7–13.
18. Villikka K, *et al.* Triazolam is ineffective in patients taking rifampicin. *Clin Pharmacol Ther* 1997; 61: 8–14.

Anticoagulants. Plasma binding of diazepam and desmethyldiazepam (nordazepam) was reduced, and free concentrations increased, immediately after intravenous *heparin*.[1]

Benzodiazepines do not usually interact with oral anticoagulants although there have been rare reports of altered anticoagulant activity.

1. Routledge PA, *et al.* Diazepam and N-desmethyldiazepam redistribution after heparin. *Clin Pharmacol Ther* 1980; 27: 528–32.

Antidepressants. It has been recommended that the dosage of alprazolam should be reduced when given with *fluvoxamine*, as concomitant use has resulted in doubling of plasma-alprazolam concentrations.[1] Since plasma concentrations of bromazepam[2] and of diazepam[3] also appear to be affected by fluvoxamine, it has been suggested that patients taking fluvoxamine who require a benzodiazepine should preferentially receive one such as lorazepam, which has a different metabolic pathway.[3] Small studies suggest that *fluoxetine* can also increase plasma concentrations of alprazolam.[4,5] Fluoxetine appears to have a similar effect on diazepam but plasma concentrations of diazepam's active metabolite desmethyldiazepam (nordazepam) are reduced and it is considered that the overall effect is likely to be minor.[6] The potential for a clinically significant interaction with *sertraline*, *paroxetine*, or *citalopram* is considered to be less.[7]

The US manufacturers have reported that alprazolam may increase the steady-state plasma concentrations of *imipramine* and *desipramine*, although the clinical significance of such changes is unknown. For a suggestion that benzodiazepines may increase the oxidation of *amineptine* to a toxic metabolite, see Effects on the Liver under Adverse Effects of Amitriptyline, p. 403.3.

Nefazodone has been reported to raise concentrations of alprazolam and triazolam, resulting in increased sedation, and impairment of psychomotor performance.[8,9] Nefazodone may inhibit the oxidative metabolism of alprazolam and triazolam. Raised concentrations of midazolam have similarly been seen when given orally with nefazodone.[10] No interaction was reported with lorazepam, which is mainly eliminated by conjugation.

For reference to an isolated report of hypothermia after administration of diazepam and *lithium*, see p. 431.3.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with benzodiazepines.

1. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994; 46: 35–9.
2. Van Harten J, *et al.* Influence of multiple-dose administration of fluvoxamine on the pharmacokinetics of the benzodiazepines bromazepam and lorazepam: a randomized crossover study. *Eur Neuropsychopharmacol* 1992; 2: 381.
3. Perucca E, *et al.* Inhibition of diazepam metabolism by fluvoxamine: a pharmacokinetic study in normal volunteers. *Clin Pharmacol Ther* 1994; 56: 471–6.
4. Lasher TA, *et al.* Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology (Berl)* 1991; 104: 323–7.
5. Greenblatt DJ, *et al.* Fluoxetine impairs clearance of alprazolam but not of clonazepam. *Clin Pharmacol Ther* 1992; 52: 479–86.
6. Lemberger L, *et al.* The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. *Clin Pharmacol Ther* 1988; 43: 412–19.
7. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; 33: 454–71.
8. Greene DS, *et al.* Coadministration of nefazodone (NEF) and benzodiazepines I: pharmacokinetic assessment. *Clin Pharmacol Ther* 1994; 55: 141.
9. Kroboth P, *et al.* Coadministration of nefazodone and benzodiazepines II: pharmacodynamic assessment. *Clin Pharmacol Ther* 1994; 55: 142.
10. Lam YWF, *et al.* Effect of antidepressants and ketoconazole on oral midazolam pharmacokinetics. *Clin Pharmacol Ther* 1998; 63: 229.

Antiepileptics. *Carbamazepine, phenobarbital,* and *phenytoin* are all inducers of hepatic drug-metabolising enzymes. Therefore, in patients receiving long-term therapy with these drugs the metabolism of benzodiazepines may be enhanced. For oral midazolam the effects of carbamazepine or phenytoin may be sufficient to virtually abolish the effects of a standard dose, with a more than 90% reduction in peak serum concentrations of the benzodiazepine.[1] Interactions between benzodiazepines and these antiepileptics are further discussed on p. 517.2 (carbamazepine) and p. 544.2 (phenytoin).

Results from a study[2] involving 66 children and adults given clobazam showed a significant increase in clobazam clearance, leading to accumulation of its principal active metabolite *N*-desmethylclobazam, in the 16 patients also taking *felbamate*. The metabolism of clobazam and *N*-desmethylclobazam was reduced by *stiripentol*, a potent hepatic enzyme inhibitor, resulting in a threefold increase in the plasma concentrations of this metabolite.[3]

Serum-clonazepam concentrations fell markedly in 4 of 8 children who had *lamotrigine* added to their therapy.[4]

Sodium valproate has been reported to displace diazepam from plasma-protein binding sites.[5] Sporadic reports exist of adverse effects when valproate is given with clonazepam[6,7] with the development of drowsiness and, more seriously, absence status epilepticus, but the existence of an interaction is considered to be unproven.[8] Drowsiness has also been reported when valproate was given with nitrazepam.[9] Use of valproate semisodium with lorazepam has resulted in raised concentrations of lorazepam due to inhibition of glucuronidation of lorazepam.[10]

1. Backman JT, *et al.* Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. *Epilepsia* 1996; 37: 253–7.
2. Contin M, *et al.* Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. *Ther Drug Monit* 1999; 21: 604–8.
3. Giraud C, *et al.* In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. *Drug Metab Dispos* 2006; 34: 608–11.
4. Eriksson A-S, *et al.* Pharmacokinetic interactions between lamotrigine and other antiepileptic drugs in children with intractable epilepsy. *Epilepsia* 1996; 37: 769–73.
5. Dhillon S, Richens A. Valproic acid and diazepam interaction in vivo. *Br J Clin Pharmacol* 1982; 13: 553–60.
6. Watson WA. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; 300: 678.
7. Browne TR. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; 300: 679.
8. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; 24: 543–56.
9. Jeavons PM, *et al.* Treatment of generalized epilepsies of childhood and adolescence with sodium valproate (Epilim). *Dev Med Child Neurol* 1977; 19: 9–25.
10. Samara EE, *et al.* Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. *J Clin Pharmacol* 1997; 37: 442–50.

Antifungals. Both a single dose and multiple doses of *ketoconazole* decreased the clearance of a single intravenous injection of chlordiazepoxide.[1] Studies[2-4] have shown that ketoconazole and *itraconazole* can have marked pharmacokinetic interactions with midazolam or triazolam and greatly increase the intensity and duration of action of these benzodiazepines. The AUC for oral midazolam was 15 times greater with ketoconazole and 10 times greater with itraconazole while peak plasma concentrations of midazolam were increased fourfold and threefold, respectively.[2] *Voriconazole* has also been reported[5] to have a similar effect on oral midazolam, increasing its AUC by about tenfold and peak plasma concentration by about fourfold. The AUC for triazolam was 22 times greater with ketoconazole and 27 times with itraconazole;[3] peak plasma concentrations of triazolam were increased about threefold by both antifungals. Ketoconazole has also been reported to have a similar but less pronounced effect on alprazolam,[6] as have itraconazole on brotizolam[7] and etizolam.[8] One study[9] indicated that the risk of interaction persists for several days after cessation of itraconazole therapy. It is recommended that the use of these antifungals with benzodiazepines should be avoided or that the dose of the benzodiazepine should be greatly reduced. A similar but less pronounced interaction occurs between *fluconazole* and oral midazolam[10] or triazolam;[11] nonetheless, the dosage of the benzodiazepine should be reduced during use together. There has also been a suggestion that oral *clotrimazole* lozenges may increase the bioavailability of oral midazolam.[12]

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; 37: 290–7.
2. Olkkola KT, *et al.* Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; 55: 481–5.
3. Varhe A, *et al.* Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; 56: 601–7.
4. Greenblatt DJ, *et al.* Interaction of triazolam and ketoconazole. *Lancet* 1995; 345: 191.
5. Saari TI, *et al.* Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Clin Pharmacol Ther* 2006; 79: 362–70.
6. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; 9: 725–34.
7. Osanai T, *et al.* Effect of itraconazole on the pharmacokinetics and pharmacodynamics of a single oral dose of brotizolam. *Br J Clin Pharmacol* 2004; 58: 476–81.
8. Araki K, *et al.* Inhibition of the metabolism of etizolam by itraconazole in humans: evidence for the involvement of CYP3A4 in etizolam metabolism. *Eur J Clin Pharmacol* 2004; 60: 427–30.
9. Neuvonen PJ, *et al.* The effect of ingestion time interval on the interaction between itraconazole and triazolam. *Clin Pharmacol Ther* 1996; 60: 326–31.
10. Ahonen J, *et al.* Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. *Eur J Clin Pharmacol* 1997; 51: 415–19.
11. Varhe A, *et al.* Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. *Br J Clin Pharmacol* 1996; 42: 465–70.
12. Shord SS, *et al.* Effects of oral clotrimazole troches on the pharmacokinetics of oral and intravenous midazolam. *Br J Clin Pharmacol* 2010; 69: 160–6.

Antihistamines. A reduction in temazepam metabolism by *diphenhydramine* may have contributed to perinatal death after ingestion of these drugs by the mother.[1]

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; 313: 1417–18.

Antivirals. The NNRTIs *delavirdine* and *efavirenz*,[1] and HIV-protease inhibitors such as *indinavir, nelfinavir, ritonavir*,[1-4] and *saquinavir*[1,3] may inhibit the hepatic microsomal systems involved in the metabolism of some benzodiazepines. Prolonged use of protease inhibitors may also *induce* these metabolic systems; interactions may therefore be complex and difficult to predict. Monitoring and dosage adjustments for the benzodiazepine may be needed, or the combination should be avoided. Benzodiazepines which should not be used with HIV-protease inhibitors include alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, and triazolam.

1. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; 36: 1598–1613.
2. Greenblatt DJ, *et al.* Extensive impairment of triazolam and alprazolam clearance by short-term low-dose ritonavir: the clinical dilemma of concurrent inhibition and induction. *J Clin Psychopharmacol* 1999; 19: 293–6.
3. Greenblatt DJ, *et al.* Alprazolam-ritonavir interaction: implications for product labeling. *Clin Pharmacol Ther* 2000; 67: 335–41.
4. Greenblatt DJ, *et al.* Differential impairment of triazolam and zolpidem clearance by ritonavir. *J Acquir Immune Defic Syndr* 2000; 24: 129–36.
5. Palkama VJ, *et al.* Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam. *Clin Pharmacol Ther* 1999; 66: 33–9.

Beta blockers. A clear pattern of interactions between benzodiazepines and beta blockers has not emerged. *Propranolol* may inhibit the metabolism of diazepam[1,2] and bromazepam,[3] and *metoprolol* may inhibit the metabolism of diazepam[1-4] or bromazepam[5] to some extent, although in many cases the effect on pharmacokinetics and pharmacodynamics is unlikely to be of clinical significance. No significant pharmacokinetic interaction has been seen between propranolol and alprazolam,[2] lorazepam,[2] or oxazepam,[6] although the rate of alprazolam absorption may be decreased.[2] Similarly no pharmacokinetic interaction has been seen between *atenolol* and diazepam,[1] *labetalol* and oxazepam,[6] or metoprolol and lorazepam.[5]

1. Hawksworth G, *et al.* Diazepam/β-adrenoceptor antagonist interactions. *Br J Clin Pharmacol* 1984; 17: 69S–76S.
2. Ochs HR, *et al.* Propranolol interactions with diazepam, lorazepam, and alprazolam. *Clin Pharmacol Ther* 1984; 36: 451–5.
3. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; 41: 562–70.
4. Klotz U, Reimann IW. Pharmacokinetic and pharmacodynamic interaction study of diazepam and metoprolol. *Eur J Clin Pharmacol* 1984; 26: 223–6.
5. Scott AK, *et al.* Interaction of metoprolol with lorazepam and bromazepam. *Eur J Clin Pharmacol* 1991; 40: 405–9.
6. Sonne J, *et al.* Single dose pharmacokinetics and pharmacodynamics of oral oxazepam during concomitant administration of propranolol and labetalol. *Br J Clin Pharmacol* 1990; 29: 33–7.

Calcium-channel blockers. Peak plasma concentrations of midazolam were doubled and the elimination half-life of midazolam prolonged when given to healthy subjects receiving *diltiazem* or *verapamil*.[1] A similar interaction has been found between diltiazem and triazolam.[2,3] Concomitant use should be avoided or the dose of these benzodiazepines reduced.

1. Backman JT, *et al.* Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br J Clin Pharmacol* 1994; 37: 221–5.
2. Varhe A, *et al.* Diltiazem enhances the effects of triazolam by inhibiting its metabolism. *Clin Pharmacol Ther* 1996; 59: 369–75.
3. Kosuge K, *et al.* Enhanced effect of triazolam with diltiazem. *Br J Clin Pharmacol* 1997; 43: 367–72.

Ciclosporin. *In-vitro* studies suggested that ciclosporin could inhibit the metabolism of midazolam.[1] However, blood-ciclosporin concentrations in patients given ciclosporin to prevent graft rejection were considered too low to result in such an interaction.

1. Li G, *et al.* Is cyclosporin A an inhibitor of drug metabolism? *Br J Clin Pharmacol* 1990; 30: 71–7.

Clonidine. Anxiety was reduced and sedation was enhanced when clonidine was given with flunitrazepam for premedication.[1]

1. Kulka PJ, *et al.* Sedative and anxiolytic interactions of clonidine and benzodiazepines. *Br J Anaesth* 1994; 72 (suppl 1): 81.

Clozapine. For reports of cardiorespiratory collapse and other adverse effects in patients taking benzodiazepines and clozapine, see p. 1062.1.

Corticosteroids. The metabolism of midazolam was increased in chronic users of *glucocorticoids*,[1] perhaps due to the induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. The changes were not considered clinically relevant if midazolam was given intravenously, but might be so if it was given orally.

1. Nakajima M, *et al.* Effects of chronic administration of glucocorticoid on midazolam pharmacokinetics in humans. *Ther Drug Monit* 1999; 21: 507–13.

Digoxin. For the effects of alprazolam and diazepam on digoxin pharmacokinetics, see p. 1357.1.

Disulfiram. Evidence from healthy and alcoholic subjects suggests that chronic use of disulfiram can inhibit the metabolism of chlordiazepoxide and diazepam leading to a prolonged half-life and reduced clearance; there was little effect on the disposition of oxazepam.[1] No significant pharmacokinetic interaction occurred between disulfiram and alprazolam in alcoholic patients.[2] Temazepam toxicity, attributed to use of disulfiram with temazepam, has been reported.[3]

See also under Disulfiram, p. 2496.3.

1. MacLeod SM, *et al.* Interaction of disulfiram with benzodiazepines. *Clin Pharmacol Ther* 1978; 24: 583–9.
2. Diquet B, *et al.* Lack of interaction between disulfiram and alprazolam in alcoholic patients. *Eur J Clin Pharmacol* 1990; 38: 157–60.
3. Hardman M, *et al.* Temazepam toxicity precipitated by disulfiram. *Lancet* 1994; 344: 1231–2.

Gastrointestinal drugs. *Antacids* have variable effects on the absorption of benzodiazepines[1-6] but any resulting interaction is unlikely to be of major clinical significance.

Several studies, usually involving single doses of diazepam given to healthy subjects, have shown that *cimetidine* can inhibit the hepatic metabolism of diazepam.[7-10] The clearance of diazepam has generally been decreased and the half-life prolonged. Some studies have also shown impaired metabolic clearance of the major metabolite, desmethyldiazepam (nordazepam). Cimetidine has also been reported to inhibit the metabolism of other benzodiazepines (generally those metabolised by oxidation) including alprazolam,[11,12] bromazepam,[13] chlordiazepoxide,[14] clobazam,[15,16] flurazepam,[17] midazolam,[18] nitrazepam,[19] and triazolam.[11,12] Cimetidine does not appear to inhibit the hepatic metabolism of lorazepam,[17] oxazepam,[17] or temazepam.[20] The clinical significance of these interactions between cimetidine and benzodiazepines remains dubious, and little effect on cognitive function or degree of sedation has been shown.

Most studies have failed to find an effect of *ranitidine* on the hepatic metabolism of diazepam,[21-24] although one study[25] reported an increase in the bioavailability of a single oral dose of midazolam, and considered that an effect on hepatic clearance was more likely than an effect on absorption. These results were consistent with those of another study which showed an enhanced sedative effect of midazolam in patients pretreated with ranitidine.[26] The bioavailability of triazolam has also been increased by ranitidine.[27] Ranitidine has been reported to have no effect on the pharmacokinetics of lorazepam[22] or on the sedative effect of temazepam.[26]

Famotidine[10] or *nizatidine*[24] do not appear to inhibit the hepatic metabolism of diazepam.

Oral diazepam was absorbed more rapidly after intravenous *metoclopramide*.[28] Enhanced motility of the gastrointestinal tract was implicated. *Cisapride* may also accelerate the absorption of diazepam.[29]

Studies of continuous *omeprazole* dosage on the pharmacokinetics of a single intravenous dose of diazepam in healthy subjects indicate inhibition of diazepam metabolism in a similar manner to cimetidine.[30,31] Omeprazole decreases the clearance and prolongs the elimination half-life of diazepam; in addition both the formation and elimination of desmethyldiazepam appear to be decreased. The effects may be greater in rapid than in slow metabolisers of omeprazole[32] and vary between ethnic groups.[33] Licensed product information for *esomeprazole* states that it too may decrease diazepam clearance. The clinical significance of these interactions is unknown; however, product information for omeprazole and esomeprazole suggests that dosage reduction of diazepam may be necessary. *Lansoprazole*[34] and *pantoprazole*[35] have been reported not to affect the pharmacokinetics of diazepam.

1. Nair SG, *et al.* The influence of three antacids on the absorption and clinical action of oral diazepam. *Br J Anaesth* 1976; **48:** 1175–80.
2. Greenblatt DJ, *et al.* Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. *Clin Pharmacol Ther* 1976; **19:** 234–9.
3. Chun AHC, *et al.* Effect of antacids on absorption of clorazepate. *Clin Pharmacol Ther* 1977; **22:** 329–35.
4. Shader RI, *et al.* Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* 1978; **24:** 308–15.
5. Greenblatt DJ, *et al.* Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther* 1978; **24:** 600–9.
6. Shader RI, *et al.* Steady-state plasma desmethyldiazepam during long-term clorazepate use: effect of antacids. *Clin Pharmacol Ther* 1982; **31:** 180–3.
7. Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. *N Engl J Med* 1980; **302:** 1012–14.
8. Gough PA, *et al.* Influence of cimetidine on oral diazepam elimination with measurement of subsequent cognitive change. *Br J Clin Pharmacol* 1982; **14:** 739–42.
9. Greenblatt DJ, *et al.* Clinical importance of the interaction of diazepam and cimetidine. *N Engl J Med* 1984; **310:** 1639–43.
10. Locniskar A, *et al.* Interaction of diazepam with famotidine and cimetidine, two H_2-receptor antagonists. *J Clin Pharmacol* 1986; **26:** 299–303.
11. Abernethy DR, *et al.* Interaction of cimetidine with the triazolobenzodiazepines alprazolam and triazolam. *Psychopharmacology (Berl)* 1983; **80:** 275–8.
12. Pourbaix S, *et al.* Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1985; **23:** 447–51.
13. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
14. Desmond PV, *et al.* Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann Intern Med* 1980; **93:** 266–8.
15. Grigoleit H-G, *et al.* Pharmacokinetic aspects of the interaction between clobazam and cimetidine. *Eur J Clin Pharmacol* 1983; **25:** 139–42.
16. Pullar T, *et al.* The effect of cimetidine on the single dose pharmacokinetics of oral clobazam and N-desmethylclobazam. *Br J Clin Pharmacol* 1987; **23:** 317–21.
17. Greenblatt DJ, *et al.* Interaction of cimetidine with oxazepam, lorazepam, and flurazepam. *J Clin Pharmacol* 1984; **24:** 187–93.
18. Sanders LD, *et al.* Interaction of H2-receptor antagonists and benzodiazepine sedation: a double-blind placebo-controlled investigation of the effects of cimetidine and ranitidine on recovery after intravenous midazolam. *Anaesthesia* 1993; **48:** 286–92.
19. Ochs HR, *et al.* Cimetidine impairs nitrazepam clearance. *Clin Pharmacol Ther* 1983; **34:** 227–30.
20. Greenblatt DJ, *et al.* Noninteraction of temazepam and cimetidine. *J Pharm Sci* 1984; **73:** 399–401.
21. Klotz U, *et al.* Effect of ranitidine on the steady state pharmacokinetics of diazepam. *Eur J Clin Pharmacol* 1983; **24:** 357–60.
22. Abernethy DR, *et al.* Ranitidine does not impair oxidative or conjugative metabolism: noninteraction with antipyrine, diazepam, and lorazepam. *Clin Pharmacol Ther* 1984; **35:** 188–92.
23. Fee JPH, *et al.* Diazepam disposition following cimetidine or ranitidine. *Br J Clin Pharmacol* 1984; **17:** 617P–18P.
24. Klotz U, *et al.* Nocturnal doses of ranitidine and nizatidine do not affect the disposition of diazepam. *J Clin Pharmacol* 1987; **27:** 210–12.
25. Fee JPH, *et al.* Cimetidine and ranitidine increase midazolam bioavailability. *Clin Pharmacol Ther* 1987; **41:** 80–4.
26. Wilson CM, *et al.* Effect of pretreatment with ranitidine on the hypnotic action of single doses of midazolam, temazepam and zopiclone. *Br J Anaesth* 1986; **58:** 483–6.
27. Vanderveen RP, *et al.* Effect of ranitidine on the disposition of orally and intravenously administered triazolam. *Clin Pharm* 1991; **10:** 539–43.
28. Gamble JAS, *et al.* Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
29. Bateman DN. The action of cisapride on gastric emptying and the pharmacokinetics of oral diazepam. *Eur J Clin Pharmacol* 1986; **30:** 205–8.
30. Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. *Lancet* 1984; **i:** 969.
31. Andersson T, *et al.* Effect of omeprazole and cimetidine on plasma diazepam levels. *Eur J Clin Pharmacol* 1990; **39:** 51–4.
32. Andersson T, *et al.* Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin Pharmacol Ther* 1990; **47:** 79–85.
33. Caraco Y, *et al.* Interethnic difference in omeprazole's inhibition of diazepam metabolism. *Clin Pharmacol Ther* 1995; **58:** 62–72.
34. Lefebvre RA, *et al.* Influence of lansoprazole treatment on diazepam plasma concentrations. *Clin Pharmacol Ther* 1992; **52:** 458–63.
35. Gugler R, *et al.* Lack of pharmacokinetic interaction of pantoprazole with diazepam in man. *Br J Clin Pharmacol* 1996; **42:** 249–52.

General anaesthetics. A synergistic interaction has been found for the hypnotic effects of midazolam and *thiopental*.[1] Although midazolam failed to produce anaesthesia at the doses used, the drug caused a twofold increase in the anaesthetic potency of thiopental. Similar synergistic interactions have been seen between midazolam and both *methohexital*[2] and *propofol*.[3,4] The interaction between midazolam and propofol could not be explained solely by alteration in free-plasma concentration of either drug,[5] although a later study[6] does suggest that propofol reduces the clearance of midazolam via its inhibitory effects on the metabolism of midazolam by the cytochrome P450 isoenzyme CYP3A4. It has been reported that midazolam can produce a marked reduction in the concentration of *halothane* required for anaesthesia.[7]

1. Short TG, *et al.* Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; **66:** 13–19.
2. Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth* 1989; **63:** 109–12.
3. McClune S, *et al.* Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
4. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
5. Teh J, *et al.* Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.
6. Ramaoka N, *et al.* Propofol decreases the clearance of midazolam by inhibiting CYP3A4: an in vivo and in vitro study. *Clin Pharmacol Ther* 1999; **66:** 110–7.
7. Inagaki Y, *et al.* Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–7.

Grapefruit juice. Grapefruit juice has been reported to be able to increase the bioavailability of oral diazepam,[1] midazolam,[2,3] quazepam,[4] and triazolam[3-5] and to raise peak plasma concentrations. Repeated ingestion of grapefruit juice increased the concentration and half-life of triazolam to a greater extent than a single ingestion.[6] The clinical significance of such interactions may be of little or no practical importance.

1. Ozdemir M, *et al.* Interaction between grapefruit juice and diazepam in humans. *Eur J Drug Metab Pharmacokinet* 1998; **23:** 55–9.
2. Kupferschmidt HHT, *et al.* Interaction between grapefruit juice and midazolam in humans. *Clin Pharmacol Ther* 1995; **58:** 20–8.
3. Vanakoski J, *et al.* Grapefruit juice does not enhance the effects of midazolam and triazolam in man. *Eur J Clin Pharmacol* 1996; **50:** 501–8.
4. Sugimoto K, *et al.* Interaction between grapefruit juice and hypnotic drugs: comparison of triazolam and quazepam. *Eur J Clin Pharmacol* 2006; **62:** 209–15.
5. Hukkinen SK, *et al.* Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. *Clin Pharmacol Ther* 1995; **58:** 127–31.
6. Lilja JJ, *et al.* Effect of grapefruit juice dose on grapefruit juice-triazolam interaction: repeated consumption prolongs triazolam half-life. *Eur J Clin Pharmacol* 2000; **56:** 411–15.

Kava. A patient whose medication included alprazolam, cimetidine, and terazosin became lethargic and disoriented after starting to take kava.[1] An interaction between kava and the benzodiazepine was suspected.

1. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; **125:** 940–1.

Levodopa. For reference to the effects of benzodiazepines on levodopa, see Anxiolytics, p. 907.3.

Neuromuscular blockers. For reference to the effect of diazepam on neuromuscular blockade, see Benzodiazepines, under the Interactions of Atracurium, p. 2032.2.

Oral contraceptives. Some studies with alprazolam,[1] chlordiazepoxide,[2] and diazepam[3] have supported suggestions that oral contraceptives may inhibit the biotransformation of benzodiazepines metabolised by oxidation, although no significant pharmacokinetic alterations have occurred with clotiazepam[4] or triazolam.[1] The biotransformation of benzodiazepines metabolised by conjugation, such as lorazepam, oxazepam, or temazepam, may be enhanced[1,2] or unchanged.[3] No consistent correlation has been seen between the above pharmacokinetic changes and clinical effects. It has been noted[6] that psychomotor impairment due to oral diazepam was greater during the menstrual pause than during the 21-daily oral contraceptive cycle. This may have been due to an effect of oral contraceptives on diazepam absorption. Another study[7] noted that women taking oral contraceptives appeared to be more sensitive to psychomotor impairment after single oral doses of alprazolam, lorazepam, or triazolam, than controls. The effects of temazepam were minimal in both groups. Alterations in sedative or amnesic effect could not be established with any certainty.

1. Stoehr GP, *et al.* Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; **36:** 683–90.
2. Patwardhan RV, *et al.* Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. *Hepatology* 1983; **3:** 248–53.
3. Abernethy DR, *et al.* Impairment of diazepam metabolism by low-dose estrogen-containing oral-contraceptive steroids. *N Engl J Med* 1982; **306:** 791–2.
4. Ochs HR, *et al.* Disposition of clotiazepam: influence of age, sex, oral contraceptives, cimetidine, isoniazid and ethanol. *Eur J Clin Pharmacol* 1984; **26:** 55–9.
5. Abernethy DR, *et al.* Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther* 1983; **33:** 628–32.
6. Ellinwood EH, *et al.* Effects of oral contraceptives on diazepam-induced psychomotor impairment. *Clin Pharmacol Ther* 1984; **35:** 360–6.
7. Kroboth PD, *et al.* Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. *Clin Pharmacol Ther* 1985; **38:** 525–32.

Penicillamine. Phlebitis associated with intravenous diazepam resolved with local heat but recurred on two separate occasions after oral penicillamine.[1]

1. Brandstetter RD, *et al.* Exacerbation of intravenous diazepam-induced phlebitis by oral penicillamine. *BMJ* 1981; **283:** 525.

Probenecid. Probenecid increased the half-life of intravenous lorazepam in 9 healthy subjects.[1] Probenecid was considered to impair glucuronide formation selectively and thus the clearance of drugs like lorazepam. Probenecid has also shortened the time to induce anaesthesia with midazolam in 46 patients.[2] The effect was considered to be due to competition for plasma protein binding sites. Probenecid has also been reported[3] to reduce the clearance of nitrazepam but not of temazepam.

1. Abernethy DR, *et al.* Probenecid inhibition of acetaminophen and lorazepam glucuronidation. *Clin Pharmacol Ther* 1984; **35:** 224.
2. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Brockmeyer NH, *et al.* Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.

Smooth muscle relaxants. Intracavernosal *papaverine* produced prolonged erection in 2 patients who had been given intravenous diazepam as an anxiolytic before the papaverine.[1]

1. Vale JA, *et al.* Papaverine, benzodiazepines, and prolonged erections. *Lancet* 1991; **337:** 1552.

Tobacco smoking. The Boston Collaborative Drug Surveillance Program reported drowsiness as an adverse effect of diazepam or chlordiazepoxide less frequently in smokers than non-smokers.[1] Pharmacokinetic studies have, however, been divided between those indicating that smoking induces the hepatic metabolism of benzodiazepines and those showing no effect on benzodiazepine pharmacokinetics.[2] Hence, diminished end-organ responsiveness may in part account for the clinical effects seen. Taking large amounts of xanthine-containing beverages as well may decrease any enzyme-inducing effects of smoking.[3]

1. Boston Collaborative Drug Surveillance Program, Boston University Medical Center. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* 1973; **288:** 277–80.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
3. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.

Xanthines. There are reports of *aminophylline* given intravenously reversing the sedation from intravenous diazepam,[1-3] although not always completely[2] nor as effectively as flumazenil.[4] Blockade of adenosine receptors by aminophylline has been postulated as the mechanism of this interaction.[3,5]

Xanthine-containing beverages may be expected to decrease the incidence of benzodiazepine-induced drowsiness because of their CNS-stimulating effects and their ability to induce hepatic drug-metabolising enzymes. However, decreased drowsiness has only sometimes been seen and the actions of xanthines may themselves be decreased by heavy tobacco smoking.[6,7]

1. Arvidsson SB, *et al.* Aminophylline antagonises diazepam sedation. *Lancet* 1982; **ii:** 1467.
2. Kleindienst G, Usinger P. Diazepam sedation is not antagonised completely by aminophylline. *Lancet* 1984; **i:** 113.
3. Niemand D, *et al.* Aminophylline inhibition of diazepam sedation: is adenosine blockade of GABA-receptors the mechanism? *Lancet* 1984; **i:** 463–4.
4. Sibai AN, *et al.* Comparison of flumazenil with aminophylline to antagonise midazolam in elderly patients. *Br J Anaesth* 1991; **66:** 591–5.
5. Benauer SA, *et al.* Theophylline antagonises diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol* 1983; **25:** 743–7.
6. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.
7. Ghoneim MM, *et al.* Pharmacokinetic and pharmacodynamic interactions between caffeine and diazepam. *J Clin Psychopharmacol* 1986; **6:** 75–80.

Pharmacokinetics

Diazepam is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30 to 90 minutes of oral doses. Diazepam is rapidly absorbed when given as a rectal solution; peak plasma concentrations occur after about 10 to 30 minutes. Absorption may be erratic after intramuscular injection and lower peak plasma concentrations may be obtained compared with those after oral doses. Diazepam is highly lipid soluble and crosses the blood-brain barrier; it acts promptly on the brain, and its initial effects decrease rapidly as it is redistributed into fat depots and tissues.

Diazepam has a biphasic half-life with an initial rapid distribution phase and a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2 to 5 days of its principal active metabolite, desmethyldiazepam (nordazepam, p. 1089.3). Diazepam and desmethyldiazepam accumulate on repeated

dosage and the relative proportion of desmethyldiazepam in the body increases with long-term use. No simple correlation has been found between plasma concentrations of diazepam or its metabolites and their therapeutic effect.

Diazepam is extensively metabolised in the liver, notably via the cytochrome P450 isoenzymes CYP2C19 and CYP3A4; in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. It is excreted in the urine, mainly in the form of free or conjugated metabolites. Diazepam is 98 to 99% bound to plasma proteins.

The plasma elimination half-life of diazepam and/or its metabolites is prolonged in neonates, in the elderly, and in patients with hepatic or renal impairment. In addition to crossing the blood-brain barrier, diazepam and its metabolites also cross the placental barrier and are distributed into breast milk.

Reviews.

1. Bailey L, *et al.* Clinical pharmacokinetics of benzodiazepines. *J Clin Pharmacol* 1994; 34: 804–11.
2. Fukasawa T, *et al.* Effects of genetic polymorphism of cytochrome P450 enzymes on the pharmacokinetics of benzodiazepines. *J Clin Pharm Ther* 2007; 32: 333–41.

Absorption and plasma concentrations. *CHRONIC ORAL ADMINISTRATION.* In 36 patients given diazepam 2 to 30 mg daily for periods from one month to 10 years, plasma-diazepam concentrations were directly related to dose and inversely related to age.[1] There was a close association between the plasma concentrations of diazepam and its metabolite desmethyldiazepam and both concentrations were independent of the duration of therapy. Plasma-diazepam concentration ranges were 20 nanograms/mL to 1.01 micrograms/mL, and plasma-desmethyldiazepam concentration ranges were 55 nanograms/mL to 1.765 micrograms/mL. A similar study[2] reached the same general conclusions.

1. Rutherford DM, *et al.* Plasma concentrations of diazepam and desmethyldiazepam during chronic diazepam therapy. *Br J Clin Pharmacol* 1978; 6: 69–73.
2. Greenblatt DJ, *et al.* Plasma diazepam and desmethyldiazepam concentrations during long-term diazepam therapy. *Br J Clin Pharmacol* 1981; 1: 35–40.

RECTAL. In 6 *adults* given diazepam 10 mg orally or as a solution (*Valium injection; Roche, UK*) by rectum, mean bioavailability was 76 and 81%, respectively compared with the same dose by intravenous injection.[1] In a second study by the same group, bioavailability was considered to be lower with diazepam suppositories than with the solution given rectally.[1] Studies support the use of rectal solution rather than suppositories in children.[2,3]

1. Dhillon S, *et al.* Bioavailability of diazepam after intravenous, oral and rectal administration in adult epileptic patients. *Br J Clin Pharmacol* 1982; 13: 427–32.
2. Dhillon S, *et al.* Rectal absorption of diazepam in epileptic children. *Arch Dis Child* 1982; 57: 264–7.
3. Sonander H, *et al.* Effects of the rectal administration of diazepam. *Br J Anaesth* 1985; 57: 578–80.

Distribution into breast milk. Concentrations of diazepam and desmethyldiazepam transferred from mother to infant via breast milk have been measured.[1,2]

See also under Precautions, p. 1067.1.

1. Erkkola R, Kanto J. Diazepam and breast-feeding. *Lancet* 1972; i: 1235–6.
2. Brandt R. Passage of diazepam and desmethyldiazepam into breast milk. *Arzneimittelforschung* 1976; 26: 454–7.

The elderly. For mention of pharmacokinetics in the elderly, see under Precautions, p. 1067.2.

Hepatic impairment. For reference to the altered pharmacokinetics of diazepam in patients with hepatic impairment, see Administration in Hepatic Impairment, p. 1064.2.

Metabolism. Most benzodiazepines are highly lipophilic compounds requiring biotransformation before excretion from the body, and many form active metabolites that affect the duration of action. The benzodiazepines may be classified as long-, intermediate-, or short-acting compounds.[1]

- **Long-acting** benzodiazepines are either N_1-desalkyl derivatives (*delorazepam* and *nordazepam*) or are oxidised in the liver to N_1-desalkyl derivatives (benzodiazepines so oxidised include *chlordiazepoxide, clobazam, clorazepate, cloxazolam, diazepam, flurazepam, halazepam, ketazolam, medazepam, oxazolam, pinazepam, prazepam,* and *quazepam*). Clorazepate and prazepam may be considered as prodrugs since the metabolite is the expected active principle. Both parent drug and metabolites contribute to the activity of the other long-acting drugs. Further biotransformation of N_1-desalkylated metabolites proceeds much more slowly than for the parent drug, and they therefore accumulate in the body after a few days of treatment. The rate-limiting step of their metabolism (with the exception of the 1,5-derivatives) is C3-hydroxylation to the pharmacologically active oxazepam or its 2′-halogenated analogues.
- **Intermediate-acting** benzodiazepines are 7-nitrobenzodiazepines such as *clonazepam, flunitrazepam,* and *nitrazepam* which are metabolised by nitroreduction with no important known active metabolites.

The metabolites of long- and intermediate-acting benzodiazepines require conjugation before excretion in the urine.

- **Short-acting** benzodiazepines include the C3-hydroxylated benzodiazepines such as *lorazepam, lormetazepam, oxazepam,* and *temazepam* which undergo rapid conjugation with glucuronic acid to water-soluble inactive metabolites that are excreted in the urine, and drugs such as *alprazolam, brotizolam, estazolam, etizolam, midazolam, tofisopam,* and *triazolam* which requfre oxidation involving aliphatic hydroxylation before subsequent conjugation. Although these hydroxylated metabolites may retain pharmacological activity, they are unlikely to contribute significantly to clinical activity because of their negligible plasma concentrations and rapid inactivation by glucuronidation.

Drug-metabolising capacity is influenced by many factors including genetics, age, gender, endocrine and nutritional status, smoking, disease, and concurrent drug therapy. This results in wide interindividual variation in both parent drug concentrations and metabolite-to-parent drug ratios.

1. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; 18: 434–59.

Pregnancy. The passage of diazepam across the placenta depends in part on the relative degrees of protein binding in mother and fetus. This in turn is influenced by factors such as stage of pregnancy and plasma concentrations of free fatty acids in mother and fetus.[1-6] Adverse effects may persist in the neonate for several days after birth because of immature drug-metabolising enzymes. Competition between diazepam and bilirubin for protein binding sites could result in hyperbilirubinaemia in the neonate.[7]

For further adverse effects associated with the use of benzodiazepines during pregnancy, see under Precautions, p. 1067.3.

1. Idänpään-Heikkilä J, *et al.* Placental transfer and fetal metabolism of diazepam-Cl^{14} in early human pregnancy. *Clin Pharmacol Ther* 1971; 12: 293.
2. Kanto J, *et al.* Accumulation of diazepam and N-demethyldiazepam in the fetal blood during the labour. *Ann Clin Res* 1973; 5: 375–9.
3. Lee JN, *et al.* Serum protein binding of diazepam in maternal and foetal serum during pregnancy. *Br J Clin Pharmacol* 1982; 14: 551–4.
4. Kuhnz W, Nau H. Differences in in vitro binding of diazepam and N-desmethyldiazepam to maternal and fetal plasma proteins at birth: relation to free fatty acid concentration and other parameters. *Clin Pharmacol Ther* 1983; 34: 220–6.
5. Nau H, *et al.* Decreased serum protein binding of diazepam and its major metabolite in the neonate during the first postnatal week related to increased free fatty acid levels. *Br J Clin Pharmacol* 1984; 17: 92–8.
6. Ridd MJ, *et al.* The disposition and placental transfer of diazepam in cesarean section. *Clin Pharmacol Ther* 1989; 45: 506–12.
7. Notarianni LJ. Plasma protein binding of drugs in pregnancy and in neonates. *Clin Pharmacokinet* 1990; 18: 20–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cuadel; Daiv; Dezepan; Diactal; Dipezona; Fabotranil†; Lembrol; Plidan; Plidex T; Psicotop; Rupediz; Saromet; Valium; *Austral.*: Antenex; Ducene†; Ranzepam; Valium; Valpam; *Austria*: Gewacalm; Psychopax; Stesolid; Valium; *Belg.*: Valium; *Braz.*: Ansilive; Calmociteno; Compaz; Diazefast; Dienpax; Dienzepax; Kiatrium; Letansil†; Menostress; Noan; Pazolini†; Relapax; Santiazepam; Somaplus; Uni Diazepax; Valium; Vetansil†; *Canad.*: Diastat; Diazemuls; Novo-Dipam; Valium; Vivol†; *Chile*: Pacinax†; *Cz.*: Apaurin; Stesolid†; *Denm.*: Apozepam; Hexalid; Stesolid; Valaxona†; *Fin.*: Diapam; Medipam; Stesolid; *Fr.*: Valium; *Ger.*: Diazep†; Faustan; Stesolid†; Valiquid; Valium; Valocordin-Diazepam; *Gr.*: Apollonset; Atarviton; Mozepam; Nivalen; Reval; Stedon; Stesolid; *Hong Kong*: Antenex†; Diazemuls; Kratium; Stesolid; Syniumt; Valpam; *Hung.*: Seduxen; Stesolid†; *India*: Alzepam; Anxol; Calmod; Calmpose; Camrelease-TR; Diaclam; Diaze; Diazecalm; Dipax; Direc-2; Dizep-P; Dizep; Elcion; Juniz; Lakpam; Lori; Paciquil; Paxum; Placidox; Rec-DZ; Valium; Zepose; *Indon.*: Mentallium†; Stesolid; Trazep; Valdimex; Valisanbe; Valium; *Irl.*: Anxicalm; Diazemuls; Rimapam†; Stesolid; Valium; *Israel*: Assival; Diaz†; Stesolid†; *Ital.*: Ansiolin; Diazemuls; Micronoan; Noan; Tranquirit; Valium; Vatran; *Malaysia*: Diapine; Diapo; Valium; *Mex.*: Alboral; Arzepam; Benzymet; Ifa-Fonal; Laxyl†; Onapan†; Ortopsique; Relazepam; Sunzepan; Vallum; Zepan†; *Neth.*: Diazemuls; Stesolid; *Norw.*: Stesolid; Valium; Vival; *NZ*: D-Pam; Diazemuls†; Propam†; Stesolid; *Philipp.*: Anxiol; Nixtensyn; Pamizep; Trankil; Valium; Valzepam; *Pol.*: Neorelium; Relanium; Relsed; *Port.*: Bialzepam; Metamidol; Stesolid; Unisedil; Valium; *Rus.*: Apaurin (Апаурин); Relanium (Реланиум); Relium (Релиум); Seduxen (Седуксен); Sibazon (Сибазон); *S.Afr.*: Benzopin†; Betapam; Calmpose†; Doval; Pax; Scripto-Pam; Tranject; Valium; *Singapore*: Diapine; Diapo; Stesolid; *Spain*: Aneurol; Gobanal†; Pacium†; Stesolid; Vallum; Vincosedan; *Swed.*: Stesolid; *Switz.*: Paceum; Psychopax; Stesolid; Valium; *Thai.*: A-Zerax; Azepam†; Calmipam; Diadon; Diamed; Diano; Diapam; Diapine; Diaz; Diazeplon; Dilium; Dimed; Dipam; Ditran; Divopan; Dizan†; Dizep; Dizepam; Dizzepam; DZP2; Manodiazo; Manolium; Med-Zepam; Monozide; Pam; Popam; Ropam; Sipam; Tranolan; V Day Zepam; Valax; Valenium; Valium†; Vason†; Vescopam; Vispam; Vomed; Vorapam; Winopam; Zam; Zepam; Zepaxid; Zopam; *Turk.*: Diapam; Diazem; Lizan; Nervium; *UK*: Dialar; Diazemuls; Rimapam; Stesolid; Tensium; *Ukr.*: Relanium (Реланиум); Seduxen (Седуксен)†; *USA*: Diastat; Valium; *Venez.*: Talema; Telsomet.

Multi-ingredient Preparations. *Arg.*: Arnol; Dafne; Faradil; Pasminox Somatico; Spasmoctyl Somatico; Tratobes; *Austria*: Betamed; Harmomed; *Braz.*: Dialudon; *Chile*: Ansioval; Calmosedan; Cardiosedantol; Diapam; Multisedil; Promidan; Sedantol; Sedilit; *Fin.*: Relapamil†; Vertipam†; *Gr.*: Distedon; *India*: Depik Forte; Depik Plus; Depranil Plus; Depsol Forte; Depsol Plus; Depsonil-DZ; Dericip Plus; Diamin Plus; Diaze-P; Dizepax; Eldep Forte; Eldep-M; Eldep-Plus; Imipam; *Indon.*: Analsik; Cetalgin; Danalgin; Hedix; Metaneuron; Neurindo; Neurodial; Neuroval; Opineuron; Potensik; Proneuron; *Ital.*: Gamibetal Plus; Spasen Somatico; Spasmeridan†; Spasmomen Somatico; Valpinax; Valtrax; *Mex.*: Adepsique; Esbelcaps; Numencial; Qual; Redotex; *Rus.*: Reladorm (Реландорм); *Spain*: Ansium; Tepazepan; Tropargal; *Turk.*: Spazmo-Valibrin; *USA*: Emergent-Ez.

Pharmacopoeial Preparations

BP 2014: Diazepam Injection; Diazepam Oral Solution; Diazepam Rectal Solution; Diazepam Tablets;
USP 36: Diazepam Capsules; Diazepam Extended-release Capsules; Diazepam Injection; Diazepam Tablets.

Dichloralphenazone *(BANJ)*

Dicloralfenazona; Dikloraalifenatsoni; Dikloralfenazon; Дихлоралфеназон.

$C_{15}H_{18}Cl_6N_2O_5$=519.0

CAS — 480-30-8.

ATC — N05CC04.

ATC Vet — QN05CC04.

UNII — YYX637R279.

Pharmacopoeias. In *US.*

USP 36: (Dichloralphenazone). A white microcrystalline powder with a slight odour characteristic of cloral hydrate. Freely soluble in water, in alcohol, and in chloroform; soluble in dilute acids. It is decomposed by dilute alkalis liberating chloroform.

Profile

Dichloralphenazone dissociates when given, to form cloral hydrate and phenazone. It has the general properties of cloral hydrate (p. 1055.2), although it is less likely to cause gastric irritation after oral doses. Phenazone-induced skin eruptions may, however, occur (see p. 124.2). Dichloralphenazone is used in some countries in combination preparations mainly for the treatment of tension and vascular headaches.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Acudrin; *USA*: Epidrin; Midrin; Migragesic IDA; Migrazone; Nodolor.

Pharmacopoeial Preparations

USP 36: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Dixyrazine

Diksyratsiini; Dixirazina; Dixyrazin; Dixyrazinum; UCB-3412; Диксиразин.

2-(2-[4-[2-Methyl-3-(phenothiazin-10-yl)propyl]piperazin-1-yl]ethoxy)ethanol.

$C_{24}H_{33}N_3O_2S$=427.6

CAS — 2470-73-7.

ATC — N05AB01.

ATC Vet — QN05AB01.

UNII — 7H368W3AYC.

Profile

Dixyrazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has a piperazine side-chain. It is given for its antipsychotic, antiemetic, and sedative properties in oral doses ranging from 20 to 75 mg daily. Dixyrazine has also been given by injection.

References.

1. Larsson S, *et al.* Premedication with intramuscular dixyrazine (Esucos): a controlled double-blind comparison with morphine-scopolamine and placebo. *Acta Anaesthesiol Scand* 1988; 32: 131–4.
2. Karlsson E, *et al.* The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiol Scand* 1993; 37: 45–8.
3. Oikkonen M, *et al.* Dixyrazine premedication for cataract surgery: a comparison with diazepam. *Acta Anaesthesiol Scand* 1994; 38: 214–17.

4. Feet PO, Gökestam KG. Increased antipanic efficacy in combined treatment with clomipramine and dixyrazine. *Acta Psychiatr Scand* 1994; 89: 230–4.
5. Kokinsky E, *et al.* Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. *Acta Anaesthesiol Scand* 1999; 43: 191–5.
6. Glaser C, *et al.* Dixyrazine for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2004; 48: 1287–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dixyrazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Esucos†; *Fin.*: Esucos†; *Ital.*: Esucos.

Droperidol *(BAN, USAN, rINN)*

Droperidol; Droperidoli; Droperidolis; Droperidolum; McN-JR-4749; R-4749; Дроперидол.

1-[1-[3-(4-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]-benzimidazolin-2-one.

$C_{22}H_{22}FN_3O_2$=379.4

CAS — 548-73-2.

ATC — N05AD08.

ATC Vet — QN05AD08.

UNII — O9U0F09D5X.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Droperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dimethylformamide. Protect from light.

USP 36: (Droperidol). A white to light tan amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 140 of alcohol, 1 in 4 of chloroform, and 1 in 500 of ether. Store under nitrogen in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Uses and Administration

Droperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.2). The duration of action of droperidol has been reported to last about 2 to 4 hours although alteration of alertness may last for up to 12 hours.

One manufacturer of droperidol (*Janssen-Cilag*) voluntarily withdrew it from the market worldwide in March 2001 after reports of QT prolongation, serious ventricular arrhythmias, or sudden death in association with its use. However, in the USA, droperidol remained available from other manufacturers although its use was restricted to the management of nausea and vomiting after surgical or diagnostic procedures (p. 1814.3) in patients who fail to show an adequate response to other treatments. Droperidol subsequently returned to the UK market in 2008 from another manufacturer and its use was similarly restricted. It is also available, in some other countries, for use as a premedicant, as an adjunct in anaesthesia, and for the control of agitated patients in acute psychoses and in mania. Droperidol has been used in the management of chemotherapy-induced nausea and vomiting. It has also been used with an opioid analgesic such as fentanyl citrate to maintain patients in a state of neuroleptanalgesia in which they are calm and indifferent to the surroundings and able to cooperate with the surgeon. The longer duration of action of droperidol must be kept in mind when using it with such opioid analgesics.

For the prevention and treatment of postoperative **nausea and vomiting** a maximum initial dose of 2.5 mg intramuscularly or intravenously has been given in the USA; additional doses of 1.25 mg may be given if necessary. In the UK, an intravenous dose ranging from 625 micrograms to 1.25 mg is recommended. Doses may be given 30 minutes before the anticipated end of surgery and repeated every 6 hours as required. Elderly patients should be given doses of 625 micrograms. Lower doses are also recommended for those with hepatic or renal impairment (see below). In the UK, droperidol may also be given for the prevention of nausea and vomiting induced by morphine and its derivatives during postoperative patient-controlled analgesia: 15 to 50 micrograms of droperidol per mg of morphine, up to a maximum of 5 mg daily of droperidol, may be given intravenously.

For details of doses in children, see below.

References.
1. McKeage K, *et al.* Intravenous droperidol: a review of its use in the management of postoperative nausea and vomiting. *Drugs* 2006; 66: 2123–47.
2. Jackson CW, *et al.* Evidence-based review of the black-box warning for droperidol. *Am J Health-Syst Pharm* 2007; 64: 1174–86.

Administration in children. Droperidol may be used for the prevention and treatment of postoperative nausea and vomiting in children who fail to show an adequate response to other treatments. In the USA, those aged 2 to 12 years have been given a maximum initial dose of 100 micrograms/kg intramuscularly or intravenously. In the UK, children aged over 2 years and adolescents may be given an intravenous dose of 20 to 50 micrograms/kg, up to a maximum of 1.25 mg. Doses may be given 30 minutes before the anticipated end of surgery and repeated every 6 hours as required.

Administration in hepatic or renal impairment. UK licensed product information recommends that patients with hepatic or renal impairment should be given droperidol in doses of 625 micrograms by intravenous injection.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. There is an increased risk of cardiotoxicity and prolongation of the QT interval (see p. 1047.3) with droperidol. Droperidol should not be used in patients with known or suspected QT prolongation; it should also be used with extreme caution, if at all, in patients at risk of arrhythmias, including those with impairment of cardiac function, hypokalaemia, or other electrolyte imbalance. It is recommended that a baseline ECG is performed in all patients before use of droperidol.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies droperidol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3. The risk of arrhythmias with droperidol may be increased by other drugs that prolong the QT interval or cause electrolyte disturbances (see also under Pimozide, p. 1097.2, for further details).

Droperidol is metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4; use with inhibitors of these isoenzymes may reduce the metabolism of droperidol and prolong its action.

Pharmacokinetics

Plasma concentrations of droperidol fall rapidly after intravenous dosage and the mean elimination half-life is 134 minutes. Droperidol is 85 to 90% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP1A2 and CYP3A4, and to a lesser extent by CYP2C19, to inactive metabolites. About 75% of a dose is excreted in the urine, with 1% being excreted unchanged; 11% appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Droleptan; *Austria*: Xomolix; *Belg.*: Dehydrobenzperidol; *Braz.*: Droperdal; *Cz.*: Xomolix; *Denm.*: Dehydrobenzperidol; *Fin.*: Dehydrobenzperidol; *Fr.*: Droleptan; *Ger.*: Xomolix; *Gr.*: Dehydrobenzperidol; Droleptan; Xomolix; *Hung.*: Xomolix; *India*: Droperol; *Irl.*: Xomolix; *Neth.*: Dehydrobenzperidol; *Norw.*: Dridol; *NZ*: Droleptan; *Port.*: Dehidrobenzperidol†; Xomolix; *S.Afr.*: Inapsin; Paxical†; *Spain*: Xomolix; *Swed.*: Dridol; *UK*: Xomolix; *USA*: Inapsine†.

Multi-ingredient Preparations. *Arg.*: Disifelit; *Braz.*: Nilperidol; *Gr.*: Thalamonal.

Pharmacopoeial Preparations
BP 2014: Droperidol Injection; Droperidol Tablets;
USP 36: Droperidol Injection.

Estazolam *(USAN, rINN)*

Abbott-47631; D-40TA; Estatsolaami; Estazolamum; Эстазолам.

8-Chloro-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*]-1,4-benzodiazepine.

$C_{16}H_{11}ClN_4$=294.7

CAS — 29975-16-4.

ATC — N05CD04.

ATC Vet — QN05CD04.

UNII — 3653EQV54C.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Estazolam). A white to pale yellowish-white crystal. Practically insoluble in water and in ether; sparingly soluble in alcohol; soluble in methyl alcohol and in acetic anhydride. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Estazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given as a hypnotic in the short-term management of insomnia (p. 1033.2) in usual oral doses of 0.5 to 2 mg at night; doses of up to 4 mg may be needed in some patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Noctal; *Fr.*: Nuctalon; *Indon.*: Esilgan; *Ital.*: Esilgan; *Jpn*: Eurodin; *Mex.*: Tasedan; *Philipp.*: Esilgan; *Port.*: Kainever.

Pharmacopoeial Preparations
USP 36: Estazolam Tablets.

Eszopiclone *(USAN, rINN)*

Eszopiclona; Eszopiclonum; Эззопиклон; (*S*)-Zopiclone; (+)-Zopiclone.

(+)-(5*S*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

$C_{17}H_{17}ClN_6O_3$=388.8

CAS — 138729-47-2.

ATC — N05CF04.

ATC Vet — QN05CF04.

UNII — UZX80K71OE.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of eszopiclone:

Sleepeasy.

Profile

Eszopiclone is the (+)-isomer of zopiclone (p. 1118.1) and is used similarly as a hypnotic in the short-term management of insomnia (p. 1033.2).

The usual oral dose is 2 mg immediately before bedtime; if appropriate, the dose may be started at or increased to 3 mg. In elderly patients who have difficulty falling asleep, the initial dose is 1 mg; this may be increased to 2 mg. For elderly patients who have difficulty staying asleep, the starting dose is 2 mg.

The dose should be reduced in patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4; a starting dose not exceeding 1 mg is recommended which may then be increased to 2 mg. For doses in patients with hepatic impairment, see below.

Reviews.
1. Melton ST, *et al.* Eszopiclone for insomnia. *Ann Pharmacother* 2005; 39: 1659–66.
2. Halas CJ. Eszopiclone. *Am J Health-Syst Pharm* 2006; 63: 41–8.
3. Hair PI, *et al.* Eszopiclone: a review of its use in the treatment of insomnia. *Drugs* 2008; 68: 1415–34.
4. Morin AK, Willett K. The role of eszopiclone in the treatment of insomnia. *Adv Therapy* 2009; 26: 500–18.

Administration in hepatic impairment. The starting oral dose of eszopiclone should be reduced to 1 mg at bedtime in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild to moderate impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: 8 Horas; Inductal; Miapax; Novo Insomnium; *Chile*: Eszop; Noptic; Plessir; Valnoc; Zopinon; *China*: Wen Fei (文飞); Yi Tan Ning (伊坦宁); *India*: Fulnite; *Jpn*: Lunesta; *USA*: Lunesta.

Ethchlorvynol *(BAN, rINN)*

β-Chlorovinyl Ethyl Ethynyl Carbinol; Etclorvinol; *E*-Ethchlorvynol; Ethchlorvynol; Ethchlorvynolum; Etklooriviniol; Etklorvinol; Этхлорвинол.

1-Chloro-3-ethylpent-1-en-4-yn-3-ol.

C_7H_9ClO=144.6

CAS — 113-18-8.

ATC — N05CM08.

ATC Vet — QN05CM08.

UNII — 6EIM3851UZ.

Pharmacopoeias. In *US*.

USP 36: (Ethchlorvynol). A colourless to yellow, slightly viscous liquid having a characteristic pungent odour. It

darkens on exposure to air and light. Immiscible with water; miscible with most organic solvents. Store in airtight containers of glass or polyethylene, using polyethylene-lined closures. Protect from light.

Profile

Ethchlorvynol is a hypnotic and sedative with effects broadly similar to those of the barbiturates (see Amobarbital, p. 1037.2). It also has some anticonvulsant and muscle relaxant properties. It has been given for the short-term management of insomnia but has been largely superseded by other drugs.

Preparations

Pharmacopoeial Preparations
USP 36: Ethchlorvynol Capsules.

Ethyl Alpha-bromoisovalerate

Ethyl 2-Bromoisovalerate; Ethyl 2-Bromo-3-methylbutanoate; Ethyl 2-Bromo-3-methylbutyrate.
Alpha-bromoisovaleric Acid Ethyl Ester.
$C_7H_{13}BrO_2$=209.1
CAS — 609-12-1.

Profile

Ethyl alpha-bromoisovalerate has actions and uses similar to those of carbromal (p. 1044.1) but the use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Rus.***: Barboval (Барбовал); Valoserdin (Валосердин); ***Ukr.***: Barboval (Барбовал); Corvaldinum (Корвалдин); Corvaltab (Корвалтаб).

Ethyl Loflazepate *(rINN)*

CM-6912; Éthyle, Loflazépate d'; Ethylis Loflazepas; Loflazepato de etilo; Этил Лофлазепат.
Ethyl 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylate.
$C_{18}H_{14}ClFN_2O_3$=360.8
CAS — 29177-84-2.
ATC — N05BA18.
ATC Vet — QN05BA18.
UNII — VJB5FW9W9J.

Profile

Ethyl loflazepate is a long-acting benzodiazepine derivative with general properties similar to those of diazepam (p. 1063.2). It is used in the short-term treatment of anxiety disorders (p. 1028.1) in usual oral doses of 1 to 3 mg daily as a single dose or in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Victan; ***China***: Meilax (美乐适); ***Fr.***: Victan; ***Jpn***: Meilax; ***Mex.***: Victan; ***Port.***: Victan; ***Thai.***: Victan†.

Etifoxine Hydrochloride *(BANM, rINNM)*

Etifoxin Hydrochloride; Etifoxina, hidrocloruro de; Étifoxine, Chlorhydrate d'; Etifoxini Hydrochloridum; Hidrocloruro de etifoxina; Hoe-36801; Этифоксина Гидрохлорид.
6-Chloro-4-methyl-4-phenyl-3,1-benzoxazin-2-yl(ethyl) amine hydrochloride.
$C_{17}H_{17}ClN_2O$,HCl=337.2
CAS — 21715-46-8 (etifoxine); 56776-32-0 (etifoxine hydrochloride).
ATC — N05BX03.
ATC Vet — QN05BX03.
UNII — NBL8010WH5.

Profile

Etifoxine hydrochloride is an anxiolytic used for the short-term treatment of anxiety (p. 1028.1). It is given in usual oral doses of 150 or 200 mg daily in 2 or 3 divided doses.

References.

1. Nguyen N, *et al.* Efficacy of etifoxine compared to lorazepam monotherapy in the treatment of patients with adjustment disorders with anxiety: a double-blind controlled study in general practice. *Hum Psychopharmacol* 2006; 21: 139–49. Correction. *ibid.*: 562.
2. Zeilhofer HU. Etifoxine (Stresam) for chemotherapy-induced pain? *Pain* 2009; 147: 9–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Stresam; ***Rus.***: Strezam (Стрезам); ***S.Afr.***: Stresam; ***Ukr.***: Stresam (Стрезам).

Etizolam *(rINN)*

AHR-3219; Étizolam; Etizolamum; Y-7131; Этизолам.
4-(2-Chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine.
$C_{17}H_{15}ClN_4S$=342.8
CAS — 40054-69-1.
ATC — N05BA19.
ATC Vet — QN05BA19.
UNII — A76X10HL37.

Pharmacopoeias. In *Jpn*.

Profile

Etizolam is a short-acting benzodiazepine derivative with general properties similar to those of diazepam (p. 1063.2). It is given for the short-term treatment of insomnia (p. 1033.2) and anxiety disorders (p. 1028.1) in oral doses of up to 3 mg daily in divided doses or as a single dose at night.

References.

1. Fukasawa T, *et al.* Pharmacokinetics and pharmacodynamics of etizolam are influenced by polymorphic CYP2C19 activity. *Eur J Clin Pharmacol* 2005; 61: 791–5.
2. Kato Z, *et al.* Accidental etizolam ingestion in a child. *Pediatr Emerg Care* 2007; 23: 472–3.
3. De Candia MP, *et al.* Effects of treatment with etizolam 0.5 mg BID on cognitive performance: a 3-week, multicenter, randomized, double-blind, placebo-controlled, two-treatment, three-period, noninferiority crossover study in patients with anxiety disorder. *Clin Ther* 2009; 31: 2851–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Etizola; ***Ital.***: Depas; Pasaden; ***Jpn***: Depas.

Fabomotizole Hydrochloride *(pINNM)*

Afobazol; Afobazole; Aphobazole; CM-346; Fabomotizole, Chlorhydrate de; Fabomotizoli Hydrochloridum; Hidrocloruro de fabomotizol; Obenoxazine Hydrochloride; SM-346; Афобазола Гидрохлорид; Фабомотизола Гидрохлорид.
5-Ethoxy-2-[[2-(4-morpholinyl)ethyl]thio]-1*H*-benzimidazole Monohydrochloride.
$C_{15}H_{21}N_3O_2S$,HCl=343.9
CAS — 173352-21-1 (fabomotizole); 173352-39-1 (fabomotizole monohydrochloride).
UNII — HDO6HX6NZU.

NOTE. Afobazol is a registered trade mark in some countries and may be used to describe the dihydrochloride.

Profile

Fabomotizole is a non-benzodiazepine anxiolytic used in the treatment of anxiety disorders (p. 1028.1). It has been given orally as the dihydrochloride in a usual dose of 10 mg three times daily. A maximum of 60 mg may be given daily.

References.

1. Neznamov GG, *et al.* Aphobazol—new selective anxyolytic drug. *Zh Nevrol Psikhiatr Im S S Korsakova* 2005; 105: 35–40.
2. Medvedev VE, *et al.* Psychopharmacotherapy of anxiety disorders in patients with cardio-vascular diseases: the use of aphobazole. *Zh Nevrol Psikhiatr Im S S Korsakova* 2007; 107: 25–9.

Fluanisone *(BAN, rINN)*

Fluanison; Fluanisona; Fluanisoni; Fluanisonum; Haloanisone; MD-2028; R-2028; R-2167; Флуанизон.
4′-Fluoro-4-[4-(2-methoxyphenyl)piperazin-1-yl]butyrophenone.
$C_{21}H_{25}FN_2O_2$=356.4
CAS — 1480-19-9.
ATC — N05AD09.
ATC Vet — QN05AD09.
UNII — 1D0W98U1I4.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Fluanisone). White or almost white to buff-coloured, odourless or almost odourless crystals or powder. It exhibits polymorphism. M.p. 72 degrees to 76 degrees. Practically insoluble in water; freely soluble in alcohol, in chloroform, in ether, and in dilute solutions of organic acids. Protect from light.

Profile

Fluanisone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It has been used in the management of agitated states in psychiatric patients and as anaesthetic premedication.

Fluanisone is used in veterinary medicine for neuroleptanalgesia.

Fludiazepam *(rINN)*

Fludiazépam; Fludiazepamum; ID-540; Флудиазепам.
7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.
$C_{16}H_{12}ClFN_2O$=302.7
CAS — 3900-31-0.
ATC — N05BA17.
ATC Vet — QN05BA17.
UNII — 7F64A2K16Z.

Pharmacopoeias. In *Jpn*.

Profile

Fludiazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given in the short-term treatment of anxiety disorders (p. 1028.1) in a usual oral dose of 250 micrograms three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Erispan.

Flunitrazepam *(BAN, USAN, rINN)*

Flunitratsepaami; Flunitrazepám; Flunitrazépam; Flunitrazepamas; Flunitrazepamum; Ro-5-4200; Флунитразепам.
5-(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-1*H*-1,4-benzodiazepin-2-one.
$C_{16}H_{12}FN_3O_3$=313.3
CAS — 1622-62-4.
ATC — N05CD03.
ATC Vet — QN05CD03.
UNII — 620X0222FQ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of flunitrazepam:

Benzo; Circles; Date rape drug; Forget me drug; Forget pill; Forget-me pill; Forget-Me-Pill; Getting roached; La Rocha; La Roche; Lunch money drug; Mexican valium; Pingus; R2; R-2; Reynolds; Rib; Rick James Biatch; Roach; Roach 2; Roach-2; Roaches; Roachies; Roapies; Robutal; Rochas dos; Roche; Roches; Rolpes; Roofie; Roofies; Roopies; Rope; Rophies; Rophy; Ropies; Roples; Ropples; Row-shay; Ruffies; Ruffles; Sedexes; Wolfies.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Flunitrazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone. Protect from light.

Uses and Administration

Flunitrazepam is an intermediate- or short-acting benzodiazepine (depending on dose) with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term management of insomnia (p. 1033.2), as a premedicant in surgical procedures, and for induction of anaesthesia (p. 1899.1).

A usual oral dose for **insomnia** is 0.5 to 1 mg at night; up to 2 mg may be given if necessary. In elderly or debilitated patients the initial dose should not exceed 500 micrograms at night; up to 1 mg may be given if necessary.

A dose of 1 to 2 mg (15 to 30 micrograms/kg) has been given intramuscularly or orally for **premedication** or by slow intravenous injection for **induction** of general anaesthesia.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Abuse. A WHO review[1] concluded that flunitrazepam had a moderate abuse potential that might be higher than that of other benzodiazepines. It was reported that there was current evidence of widespread abuse of flunitrazepam among drug abusers, particularly among those who used opioids or cocaine. Flunitrazepam has also been abused at social gatherings where it is taken orally or intranasally.[2,3]

Flunitrazepam is tasteless and odourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[2-4] A 1-

mg dose may produce impairment for 8 to 12 hours.[2] Some manufacturers have incorporated a blue dye into flunitrazepam tablets to increase visibility when placed into drinks[4] but caution is still necessary as it has been reported that blue tropical drinks and punches are being used to overcome this.

1. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_856.pdf (accessed 21/08/08)
2. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59**: 1067–76.
3. National Institute on Drug Abuse. Club drugs (GHB, Ketamine, and Rohypnol) (updated July 2010). Available at: http://www.drugabuse.gov/pdf/infofacts/ClubDrugs10.pdf (accessed 12/11/10)
4. Simmons MM, Cupp MJ. Use and abuse of flunitrazepam. *Ann Pharmacother* 1998; **32**: 117–19.

Breast feeding. Concentrations in breast milk the morning after a single evening 2-mg dose of flunitrazepam were considered to be too low to produce clinical effects in breast-fed infants, although accumulation in the milk might occur after repeated use.[1]

1. Kanto J, *et al.* Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26**: 539–46.

Local reactions. Of 43 patients given a single intravenous dose of flunitrazepam 1 to 2 mg, two had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution]. However, there was little difference in the incidence of local reactions after intravenous use of flunitrazepam and diazepam in another study.[2]

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; **2**: 1384–5.
2. Mikkelsen H, *et al.* Local reactions after iv injections of diazepam, flunitrazepam and isotonic saline. *Br J Anaesth* 1980; **52**: 817–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flunitrazepam as probably porphyrinogenic; it should be prescribed only for compelling indications and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Flunitrazepam is readily absorbed from the gastrointestinal tract after oral doses. It is about 77 to 80% bound to plasma proteins. Flunitrazepam is extensively metabolised in the liver and excreted mainly in the urine as metabolites (free or conjugated). Its principal metabolites are 7-aminoflunitrazepam and *N*-desmethylflunitrazepam; *N*-desmethylflunitrazepam is reported to be pharmacologically active but less so than the parent compound. The elimination half-life of flunitrazepam is reported to be between 16 and 35 hours. Flunitrazepam crosses the placental barrier and is distributed into breast milk.

References.

1. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11**: 18–35.
2. Pariente-Khayat A, *et al.* Pharmacokinetics and tolerance of flunitrazepam in neonates and in infants. *Clin Pharmacol Ther* 1999; **66**: 136–9.

Pregnancy. Concentrations of flunitrazepam in umbilical-vein and umbilical-artery plasma were lower than those in maternal venous plasma about 11 to 15 hours after a dose of flunitrazepam 1 mg in 14 pregnant women; concentrations in amniotic fluid were lower still.[1]

1. Kanto J, *et al.* Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26**: 539–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nervocuril; Primum; Rohypnol; ***Austral.***: Hypnodorm; ***Austria***: Guttanotte; Rohypnol; Somnubene; ***Belg.***: Rohypnol; ***Braz.***: Rohydorm; Rohypnol; ***Chile***: Ipnopen; ***Denm.***: Flunipam; ***Fr.***: Narcozep; Rohypnol; ***Ger.***: Fluninoc†; Rohypnol; ***Gr.***: Hipnosedon; Ilman; Neo Nifalium; Nilium; Stedonil; Vulbegal; ***Hong Kong***: Flunita; Rohypnol; ***Irl.***: Rohypnol; ***Israel***: Hypnodorm; ***Ital.***: Roipnol; Valsera; ***Mex.***: Rohypnol; ***Norw.***: Flunipam†; ***Pol.***: Rohypnol†; ***Port.***: Rohypnol†; ***Rus.***: Rohypnol (Рогипнол); ***S.Afr.***: Hypnor; Insom†; Rohypnol; ***Spain***: Rohipnol†; ***Swed.***: Fluscand†; ***Switz.***: Rohypnol; ***Thai.***: Rohypnol†.

Flupentixol *(BAN, rINN)*

Flupenthixol; Flupentiksoli; Flupentixolum; LC-44; N-7009; Флупентиксол.

(*Z*)-2-[4-[3-(2-Trifluoromethylthioxanthen-9-ylidene)propyl]piperazin-1-yl]ethanol.

$C_{23}H_{25}F_3N_2OS$=434.5

CAS — 2709-56-0.

ATC — N05AF01.

ATC Vet — QN05AF01.

UNII — FA0UYH6QUO.

Flupentixol Decanoate *(BANM, rINNM)*

cis-Flupenthixol Decanoate; Decanoato de flupentixol; Flupenthixol Decanoate; (*Z*)-Flupenthixol Decanoate; Flupentiksol Dekanoat; Flupentixol, Décanoate de; Flupentixol, decanoato de; Flupentixoli Decanoas; Флупентиксола Деканоат.

$C_{33}H_{43}F_3N_2O_2S$=588.8

CAS — 30909-51-4.

ATC — N05AF01.

ATC Vet — QN05AF01.

UNII — 3B2FE28C1W.

Pharmacopoeias. In *Br.*

BP 2014: (Flupentixol Decanoate). A yellow viscous oil. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Store at a temperature below -15 degrees and protect from light.

Flupentixol Hydrochloride *(BANM, rINNM)*

Flupenthixol Dihydrochloride; Flupenthixol Hydrochloride; Flupentiksol Dihidroklorür; Flupentiksolidihydrokloridi; Flupentiksolio dihidrochloridas; Flupentixol, Chlorhydrate de; Flupentixol, dichlorhydrate de; Flupentixol, hidrocloruro de; Flupentixol-dihidroklorid; Flupentixol-dihydrochlorid; Flupentixoldihydroklorid; Flupentixoli dihydrochloridum; Flupentixoli Hydrochloridum; Hidrocloruro de flupentixol; Флупентиксола Гидрохлорид.

$C_{23}H_{25}F_3N_2OS,2HCl$=507.4

CAS — 2413-38-9.

ATC — N05AF01.

ATC Vet — QN05AF01.

UNII — 96L0Z069N1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flupentixol Dihydrochloride; Flupentixol Hydrochloride BP 2014). A white or almost white powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Enever RP, *et al.* Flupenthixol dihydrochloride decomposition in aqueous solution. *J Pharm Sci* 1979; **68**: 169–71.
2. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32**: 25–9.

Uses and Administration

Flupentixol is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain. Flupentixol is used mainly in the treatment of schizophrenia (p. 1031.3) and other psychoses. Unlike chlorpromazine, an activating effect has been ascribed to flupentixol, and it is not indicated in overactive or manic patients. Flupentixol has also been used for its antidepressant properties.

Flupentixol is given orally as the hydrochloride although doses are expressed in terms of the base; flupentixol hydrochloride 3.5 mg is equivalent to about 3 mg of flupentixol. Flupentixol is also given as the longer-acting decanoate ester by deep intramuscular injection. The long-acting preparation available in the UK contains flupentixol decanoate as the *cis*(*Z*)-isomer (see Action, below) and doses are expressed in terms of the amount of *cis*(*Z*)-flupentixol decanoate.

The usual initial *oral* dose for the treatment of **psychoses** is the equivalent of 3 to 9 mg of flupentixol twice daily adjusted according to response; the maximum recommended daily dose is 18 mg. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If given by *deep intramuscular* injection, an initial test dose of 20 mg of the *decanoate*, as 1 mL of a 2% oily solution, is used. Then, after at least 7 days and according to response, this may be followed by doses of 20 to 40 mg every 2 to 4 weeks. Shorter dosage intervals or greater amounts may be required according to the patient's response. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If doses greater than 40 mg (2 mL) are considered necessary they should be divided between 2 separate injection sites. Another means of reducing the volume of fluid to be injected in patients requiring high-dose therapy is to give an injection containing 100 or 200 mg/mL of the decanoate (10 or 20%). The usual maintenance dose is between 50 mg every 4 weeks and 300 mg every 2 weeks but doses of up to 400 mg weekly have been given in severe or resistant cases.

Flupentixol has also been given as the hydrochloride for the treatment of mild to moderate **depression**, with or without anxiety (p. 398.1). The usual initial *oral* dose expressed in terms of the equivalent amount of flupentixol is 1 mg (0.5 mg in the elderly) daily, increased after 1 week to 2 mg (1 mg in the elderly) and then to a maximum of 3 mg (1.5 mg in the elderly) daily. Doses above 2 mg (1 mg in the elderly) should be given in 2 divided doses. The last dose of the day should be given no later than 4 p.m. and if no effect has been noted within 1 week of reaching the maximum dose, treatment should be withdrawn.

Action. Patients with acute schizophrenic illnesses taking α-flupentixol[(*Z*)-flupentixol or *cis*-flupentixol] improved more after 3 weeks than patients who were taking equal doses of β-flupentixol[(*E*)-flupentixol or *trans*-flupentixol] or a placebo.[1] The α-isomer had more effect on the positive symptoms of the disease; this difference was less apparent for the negative symptoms. The difference in activity between the isomers was attributed to the greater dopamine-receptor blocking activity of the α-isomer rather than to differences in distribution.[2]

1. Johnstone EC, *et al.* Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet* 1978; **i**: 848–51.
2. Crow TJ, Johnstone EC. Mechanism of action of neuroleptic drugs *Lancet* 1978; **i**: 1050.

Adverse Effects and Treatment

As for Chlorpromazine, p. 1047.2. Flupentixol is less likely to cause sedation, but extrapyramidal effects are more frequent.

Sudden death. Sudden death has been reported in 3 patients given depot injections of flupentixol decanoate.[1]

1. Turbott J, Smeeton WMI. Sudden death and flupenthixol decanoate. *Aust N Z J Psychiatry* 1984; **18**: 91–4.

Precautions

As for Chlorpromazine, p. 1050.3. Flupentixol is not recommended in states of excitement or overactivity including mania.

When flupentixol is used in the management of depression, patients should be closely monitored during early therapy until significant improvement in depression is seen because suicide is an inherent risk in depressed patients. For further details, see Depression, p. 398.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flupentixol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Flupentixol is readily absorbed from the gastrointestinal tract after oral use and is probably subject to first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous metabolites; there is evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after estimated equivalent doses of the intramuscular depot preparation. Moreover, there is very wide intersubject variation in plasma concentrations of flupentixol, but, in practice, no simple correlation has been found between the therapeutic effect and plasma concentrations of flupentixol and its metabolites. After oral doses, peak plasma concentrations occur in about 4 hours and the biological half-life is about 35 hours. Paths of metabolism of flupentixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. Flupentixol is more than 95% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Flupentixol crosses the placental barrier and small amounts have been detected in breast milk.

The decanoate ester of flupentixol is very slowly absorbed from the site of intramuscular injection and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to flupentixol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fluanxol; ***Austria***: Fluanxol; ***Belg.***: Fluanxol; ***Canad.***: Fluanxol; ***Chile***: Fluanxol; ***China***: Fluanxol (芋岚素); ***Cz.***: Fluanxol; ***Denm.***: Fluanxol; ***Fin.***: Fluanxol; ***Fr.***: Fluanxol; ***Ger.***: Fluanxol; ***Gr.***: Fluanxol; ***Hong Kong***: Fluanxol; ***Hung.***: Fluanxol; ***India***: Fluanxol; Flupen; Novoxit; ***Irl.***: Depixol; Fluanxol; ***Israel***: Fluanxol; ***Malaysia***: Fluanxol; ***Mex.***: Fluanxol; ***Neth.***: Fluanxol; ***Norw.***: Fluanxol; ***NZ***: Fluanxol; ***Philipp.***: Fluanxol; ***Pol.***: Fluanxol; ***Port.***: Fluanxol; ***Rus.***: Fluanxol (Флюанксол); ***S.Afr.***: Fluanxol; ***Singapore***: Fluanxol; ***Swed.***: Fluanxol; ***Switz.***: Fluanxol; ***Thai.***: Fluanxol; ***Turk.***: Fluanxol; ***UK***: Depixol; Fluanxol; ***Ukr.***: Fluanxol (Флюанксол).

Multi-ingredient Preparations. ***Austria***: Deanxit; ***Belg.***: Deanxit; ***China***: Deanxit (黛力新); ***Hong Kong***: Anfree; Danxipress; Deanxit; Quali-Xit; ***India***: Ambulax-FM; Deanxit; Delewal; Denxol; Flupen-M; Forcalm; Franxit; Fycida-M; Melicen-FP; Meliyos; Melthix; Metflu; ***Singapore***: Deanxit; ***Spain***: Deanxit; ***Switz.***: Deanxit; ***Thai.***: Deanxit.

Pharmacopoeial Preparations
BP 2014: Flupentixol Injection.

Fluphenazine *(BAN, rINN)*

Flufenatsiini; Flufenazin; Flufenazina; Fluphénazine; Fluphenazinum; Флуфеназин.

2-[4-[3-(2-Trifluoromethylphenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

$C_{22}H_{26}F_3N_3OS$=437.5

CAS — 69-23-8.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — S79426A412.

Fluphenazine Decanoate *(BANM, rINNM)*

Decanoato de flufenazina; Flufenatsiinidekanoaatti; Flufenazin Dekanoat; Flufenazina, decanoato de; Flufenazindekanoat; Flufenazin-dekanoát; Flufenazine-dekanoát; Flufenazino dekanoatas; Fluphenazindecanoat; Fluphénazine, Décanoate de; Fluphenazini Decanoas; Флуфеназина Деканоат.

$C_{32}H_{44}F_3N_3O_2S$=591.8

CAS — 5002-47-1.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — FMU62K1L3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Fluphenazine Decanoate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Fluphenazine Decanoate). Store in airtight containers. Protect from light.

Fluphenazine Enantate *(BANM, rINNM)*

Enantato de flufenazina; Flufenatsiinienantaatti; Flufenazina, enantato de; Flufenazinenantat; Flufenazin-enantát; Flufenazino enantatas; Fluphénazine, Enantate de; Fluphenazine Enanthate; Fluphenazine Heptanoate; Fluphenazinenantat; Fluphenazini Enantas; Флуфеназина Энантат.

$C_{29}H_{38}F_3N_3O_2S$=549.7

CAS — 2746-81-8.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — QSB34YF0W9.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Fluphenazine Enantate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Fluphenazine Enanthate). A pale yellow to yellow-orange, clear to slightly turbid, viscous liquid having a characteristic odour. Insoluble in water; soluble 1 in less than 1 of alcohol and of chloroform and 1 in 2 of ether. Stable in air at room temperature but unstable in strong light. Store in airtight containers. Protect from light.

Fluphenazine Hydrochloride *(BANM, rINNM)*

Flufenatsiinihydrokloridi; Flufenazina, hidrocloruro de; Flufenazin-dihydrochlorid; Flufenazin-hidroklorid; Flufenazinhydroklorid; Flufenazino hidrochloridas; Flufenazyny chlorowodorek; Fluphenazindihydrochlorid; Fluphénazine, Chlorhydrate de; Fluphenazine Dihydrochloride; Fluphenazini Dihydrochloridum; Fluphenazini Hydrochloridum; Hidrocloruro de flufenazina; Флуфеназина Гидрохлорид.

$C_{22}H_{26}F_3N_3OS,2HCl$=510.4

CAS — 146-56-5.
ATC — N05AB02.
ATC Vet — QN05AB02.
UNII — ZOU145W1XL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Fluphenazine Dihydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 1.9 to 2.4. Protect from light.

USP 36: (Fluphenazine Hydrochloride). A white or nearly white, odourless crystalline powder. Soluble 1 in 1.4 of water and 1 in 6.7 of alcohol; slightly soluble in acetone and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Fluphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain. Fluphenazine is used in the treatment of psychiatric disorders including schizophrenia (below) and mania (see Bipolar Disorder, p. 397.2). It has also been used for severe anxiety and behavioural disturbances. Fluphenazine is given orally or sometimes by intramuscular injection as the hydrochloride; for both routes, doses are expressed in terms of fluphenazine hydrochloride. It is also given orally as the maleate, doses being expressed in terms of fluphenazine. The longer-acting decanoate or enantate esters of fluphenazine are given by intramuscular or sometimes subcutaneous injection; for both esters, doses are expressed in terms of the ester.

The usual initial *oral* dose of the hydrochloride for the treatment of schizophrenia, mania, and other **psychoses** is 2.5 to 10 mg daily given in divided doses every 6 to 8 hours; the dose is then increased according to response up to a usual maximum of 20 mg daily, although higher doses have occasionally been given. Dosage may subsequently be reduced to a usual maintenance dose of 1 to 5 mg daily which may be given as a single dose. A lower initial dose of 1 to 2.5 mg daily, increased according to response, is recommended in the elderly. Treatment is sometimes started with an initial *intramuscular* injection of 1.25 mg of the hydrochloride adjusted thereafter according to response. The usual initial intramuscular dose is 2.5 to 10 mg daily given in divided doses every 6 to 8 hours. In general the required parenteral doses of fluphenazine hydrochloride have been found to be about one-third to one-half of those given orally. When symptoms are controlled, oral maintenance therapy may be substituted.

The long-acting decanoate or enantate esters of fluphenazine are usually given by deep intramuscular injection and are used mainly for the *maintenance* treatment of patients with schizophrenia or other chronic psychoses. The onset of action is usually within 1 to 3 days of injection and significant effects on psychosis are usually evident within 2 to 4 days. An initial dose of fluphenazine decanoate 12.5 mg (6.25 mg in the elderly) is given intramuscularly. Subsequent adjustments in the amounts and the dosage interval should be made according to the patient's response; the amounts required may range from 12.5 to 100 mg and the intervals required may range from 2 weeks to 5 or 6 weeks. Lower doses may be possible in some patients (see Schizophrenia, below). If doses greater than 50 mg are considered necessary, cautious increments should be made in steps of 12.5 mg. The enantate ester of fluphenazine has been given in a similar dose range at intervals of 1 to 3 weeks.

Schizophrenia. References[1-3] to fluphenazine decanoate in schizophrenia (p. 1031.3) indicating that low doses (10 mg or less every 2 weeks) may be effective in some patients. Use of standard doses at greater intervals (6 weeks) has also been tried.[4] A systematic review of the use of depot fluphenazine in schizophrenia found little advantage over oral use in terms of compliance.[5] Another systematic review[6] considered that although oral fluphenazine is inexpensive and widely available, other drugs may be preferable because of its adverse effects.

1. Kane JM, *et al.* Low-dose neuroleptic treatment of outpatient schizophrenics: I preliminary results for relapse rates. *Arch Gen Psychiatry* 1983; 40: 893–6.
2. Marder SR, *et al.* Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. *Arch Gen Psychiatry* 1987; 44: 581–21.
3. Hogarty GE, *et al.* Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia: results of a two-year controlled study. *Arch Gen Psychiatry* 1988; 45: 797–805.
4. Carpenter WT, *et al.* Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry* 1999; 156: 412–18.
5. David A, *et al.* Depot fluphenazine decanoate and enanthate for schizophrenia. *Available in The Cochrane Database of Systematic Reviews*; Issue 2. Chichester: John Wiley; 2004 (accessed 14/04/05).
6. Matar HE, AlMerie MQ. Oral fluphenazine versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Tourette's syndrome. Fluphenazine has been tried as an alternative to standard dopamine antagonists such as haloperidol or pimozide in the symptomatic management of Tourette's syndrome (p. 1030.1).

Adverse Effects and Treatment

As for Chlorpromazine, p. 1047.2. Fluphenazine is less likely to cause sedation, hypotension, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects.

Convulsions. For mention of fluphenazine as one of the antipsychotics suitable for patients at risk of seizures, see p. 1047.3.

Effects on the liver. A patient developed jaundice 17 days after the first of 3 injections of a depot antipsychotic containing fluphenazine decanoate given over a 2-week period.[1] Indicators of severe liver toxicity, with extreme hyperbilirubinaemia and raised liver enzyme values, were noted and he remained very ill for the next 4 months. The patient showed cross-sensitivity to haloperidol but not to flupentixol.

See also under Chlorpromazine, p. 1049.1.

1. Kennedy P. Liver cross-sensitivity to antipsychotic drugs. *Br J Psychiatry* 1983; 143: 312.

Overdosage. A patient who took about 30 fluphenazine hydrochloride 2.5-mg tablets was treated with gastric lavage.[1] Twenty hours after hospital admission he had difficulty in breathing due to spasm of the respiratory muscles; other very severe extrapyramidal adverse effects were also present. Muscle spasm was controlled by diazepam.

There were few adverse effects in a patient given intramuscular fluphenazine decanoate 50 mg every 4 hours, instead of the intended 4 weeks, to a total of 1050 mg.[2] About 3 weeks after the period of overdosage the patient had some degree of hypothermia and tachycardia, and after a further week parkinsonian signs appeared. No specific treatment was given.

1. Ladhani FM. Severe extrapyramidal manifestations following fluphenazine overdose. *Med J Aust* 1974; 2: 26.
2. Cheung HK, Yu ECS. Effect of 1050 mg fluphenazine decanoate given intramuscularly over six days. *BMJ* 1983; 286: 1016–17.

Precautions

As for Chlorpromazine, p. 1050.3. Fluphenazine may exacerbate depression and therefore it is contra-indicated in severely depressed patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluphenazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pregnancy. A neonate delivered to a mother who had received fluphenazine hydrochloride 10 to 20 mg daily throughout pregnancy had nasal congestion with severe rhinorrhoea, respiratory distress, vomiting, and extrapyramidal symptoms. Respiratory symptoms appeared to respond to pseudoephedrine.

1. Nath SP, *et al.* Severe rhinorrhea and respiratory distress in a neonate exposed to fluphenazine hydrochloride prenatally. *Ann Pharmacother* 1996; 30: 35–7.

Interactions

As for Chlorpromazine, p. 1051.3. Fluphenazine is metabolised by the cytochrome P450 isoenzyme CYP2D6 and is itself an inhibitor of this enzyme; other substrates or inhibitors of CYP2D6 may increase plasma concentrations and prolong the effects of fluphenazine.

Pharmacokinetics

Fluphenazine hydrochloride is absorbed after oral doses, and has a reported plasma half-life of 14.7 hours. Fluphenazine decanoate and fluphenazine enantate are very slowly absorbed from the site of subcutaneous or intramuscular injection. They both gradually release fluphenazine into the body and are therefore suitable for use as depot injections. The cytochrome P450 isoenzyme CYP2D6 is involved in fluphenazine metabolism. The plasma half-life of fluphenazine decanoate has been reported to be 6 to 9 days after intramuscular injection.

References[1-4] to the pharmacokinetics of fluphenazine.

The plasma half-life of fluphenazine after a single dose was 14.7 hours in 1 patient given the hydrochloride orally and 14.9 and 15.3 hours in 2 patients given the

hydrochloride by intramuscular injection.[1] The half-life was 3.6 and 3.7 days in 2 patients given the enantate intramuscularly and 9.6 and 6.8 days in 2 patients given the decanoate intramuscularly. Peak plasma-fluphenazine concentrations occurred earlier in patients given fluphenazine decanoate compared with those who received the enantate. Fluphenazine sulfoxide and 7-hydroxyfluphenazine were identified in the urine and faeces.

1. Curry SH, *et al.* Kinetics of fluphenazine after fluphenazine dihydrochloride, enanthate and decanoate administration to man. *Br J Clin Pharmacol* 1979; 7: 325–31.
2. Wistedt B, *et al.* Slow decline of plasma drug and prolactin levels after discontinuation of chronic treatment with depot neuroleptics. *Lancet* 1981; i: 1163.
3. Midha KK, *et al.* Kinetics of oral fluphenazine disposition in humans by GC-MS. *Eur J Clin Pharmacol* 1983; 25: 709–11.
4. Marder SR, *et al.* Plasma levels of parent drug and metabolites in patients receiving oral and depot fluphenazine. *Psychopharmacol Bull* 1989; 25: 479–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Modecate; *Austria*: Dapotum†; *Braz.*: Flufenan; *Canad.*: Modecate; *Chile*: Modecate; *China*: Deca (癸加); *Cz.*: Afluditen; Moditen; *Denm.*: Siqualone†; *Fin.*: Siqualone; *Fr.*: Modecate; Moditen†; *Ger.*: Dapotum†; Lyogen; *Hong Kong*: Modecate†; *Hung.*: Moditen; *India*: Anatensol; Fludecan; FPZ; *Indon.*: Anatensol†; Modecate†; *Irl.*: Modecate; *Israel*: Fludecate; *Ital.*: Moditen; *Jpn*: Flumezin; *Malaysia*: Deca; Monasan; *Mex.*: Siqualine; *Neth.*: Anatensol; *NZ*: Anatensol; Modecate; *Philipp.*: Fluxim; Modezine; Shrizine†; Sydepres†; *Port.*: Anatensol; Phenazin†; *Rus.*: Moditen (Модитен); *S.Afr.*: Fludecate†; Modecate; *Spain*: Modecate; *Swed.*: Siqualone; *Switz.*: Dapotum†; *Thai.*: Deca; Flucine; Pharnazine; *Turk.*: Prolixin; *UK*: Modecate; *Ukr.*: Moditen (Модитен); *Venez.*: Moditen.

Multi-ingredient Preparations. *Braz.*: Diserim; *Chile*: Motitrel†; *Indon.*: Motival†; *Irl.*: Motival†; *Ital.*: Dominans; *Mex.*: Motival; *S.Afr.*: Motival†; *Thai.*: Cetavol.

Pharmacopoeial Preparations
BP 2014: Fluphenazine Decanoate Injection; Fluphenazine Tablets;
USP 36: Fluphenazine Decanoate Injection; Fluphenazine Enanthate Injection; Fluphenazine Hydrochloride Elixir; Fluphenazine Hydrochloride Injection; Fluphenazine Hydrochloride Oral Solution; Fluphenazine Hydrochloride Tablets.

Flurazepam *(BAN, rINN)*

Fluratsepaaml; Flurazépam; Flurazepamum; Флуразепам.
7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one.
$C_{21}H_{23}ClFN_3O$=387.9
CAS — 17617-23-1.
ATC — N05CD01.
ATC Vet — QN05CD01.
UNII — IHP475989U.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of flurazepam:
Downs.

Pharmacopoeias. In *Jpn.*

Flurazepam Monohydrochloride

(BANM, rINNM)

Fluratsepaamimonohydrokloridi; Flurazepam hydrochlorid; Flurazépam, Monochlorhydrate de; Flurazepam, monohidrocloruro de; Flurazepami Hydrochloridum; Flurazepami Monohydrochloridum; Flurazepám-monohidroklorid; Flurazepammonohydroklorid; Flurazepamo monohidrochloridas; Monochidrocloruro de flurazepam; Флуразепама Моногидрохлорид.
$C_{21}H_{23}ClFN_3O.HCl$=424.3
CAS — 36105-20-1.
ATC — N05CD01.
ATC Vet — QN05CD01.
UNII — 7C4JH842U.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Flurazepam Monohydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.0. Protect from light.

Flurazepam Dihydrochloride *(BANM, rINNM)*

Dihidrocloruro de flurazepam; Flurazépam, Dichlorhydrate de; Flurazepam, dihidrocloruro de; Flurazepam Hydrochloride *(USAN)*; Flurazepamhydrochlorid; Flurazepami Dihydrochloridum; NSC-78559; Ro-5-6901; Флуразепама Дигидрохлорид.
$C_{21}H_{23}ClFN_3O.2HCl$=460.8
CAS — 1172-18-5.
ATC — N05CD01.
ATC Vet — QN05CD01.
UNII — 756RDM536M.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Flurazepam Hydrochloride). An off-white to yellow crystalline powder. Is odourless or has a slight odour. Soluble 1 in 2 of water, 1 in 4 of alcohol, 1 in 90 of chloroform, 1 in 3 of methyl alcohol, 1 in 69 of isopropyl alcohol, 1 in 5000 of ether and of petroleum spirit, and 1 in 2500 of benzene. A solution in water is acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Flurazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (p. 1033.2).

In the USA flurazepam is given as the dihydrochloride and doses are expressed in terms of this salt; flurazepam dihydrochloride 30 mg is equivalent to about 25.3 mg of flurazepam. Doses of 15 to 30 mg orally at night are given. In the UK flurazepam is given as the monohydrochloride although doses are expressed in terms of the base; flurazepam monohydrochloride 32.8 mg is equivalent to about 30 mg of flurazepam. Oral doses equivalent to 15 to 30 mg of flurazepam at night are given.

A maximum initial dose of 15 mg has been suggested for elderly or debilitated patients.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 7.5 to 15 mg of flurazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Effects on the liver. Reports of cholestatic jaundice after the use of flurazepam.[1,2]

1. Pang MR, *et al.* Cholestatic jaundice associated with flurazepam hydrochloride. *Ann Intern Med* 1978; 89: 363–4.
2. Reynolds R, *et al.* Cholestatic jaundice induced by flurazepam hydrochloride. *Can Med Assoc J* 1981; 124: 893–4.

Effects on taste. Flurazepam had been reported to cause dysgeusia.[1]

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983 (June): 368–71.

Renal impairment. Five patients on maintenance haemodialysis developed encephalopathy attributed to flurazepam and diazepam.[1]

1. Tadob I, Needle M. Drug-induced encephalopathy in patients on maintenance haemodialysis. *Lancet* 1976; ii: 704–5.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Flurazepam is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 30 to 60 minutes of oral doses. It undergoes extensive first-pass metabolism and is excreted in the urine, mainly as conjugated metabolites. The major active metabolite, *N*-desalkylflurazepam, is reported to have a half-life ranging from 47 to 100 hours or more and to cross the placental barrier.

Metabolism. The metabolism of flurazepam was studied in 4 healthy male subjects given 30 mg daily for 2 weeks.[1] A hydroxyethyl metabolite was present in the blood shortly after a dose. The *N*-desalkyl metabolite, the major metabolite in the blood, had a half-life ranging from 47 to 100 hours. Steady-state concentrations were reached after 7 to 10 days and were about 5 to 6 times greater than those seen on day 1. Results from a study in 3 patients indicated that some metabolism of flurazepam may occur in the small bowel mucosa.[2]

1. Kaplan SA, *et al.* Blood level profile in man following chronic oral administration of flurazepam hydrochloride. *J Pharm Sci* 1973; 62: 1932–5.
2. Mahon WA, *et al.* Metabolism of flurazepam by the small intestine. *Clin Pharmacol Ther* 1977; 22: 228–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Staurodorm; *Braz.*: Dalmadorm; *Canad.*: Dalmane; Novo-Flupam†; Som Pam; Somnol†; *Ger.*: Dalmadorm; Staurodorm Neu; *Gr.*: Dalmadorm; *Hong Kong*: Dalmadorm; *India*: Fluracap; Fluraz; Nindral; *Indon.*: Dalmadorm; *Irl.*: Dalmane; Dalmapam; *Ital.*: Dalmadorm; Felison; Flunox; Remdue; Valdorm; *Jpn*: Benozil; *Neth.*: Dalmadorm; *Port.*: Dalmadorm; Morfex; *S.Afr.*: Dalmadorm†; *Singapore*: Dalmadorm†; *Spain*: Dormodor; *Switz.*: Dalmadorm; *Thai.*: Dalmadorm†; *UK*: Dalmane; *USA*: Dalmane†; *Venez.*: Fluralema.

Pharmacopoeial Preparations
BP 2014: Flurazepam Capsules;
USP 36: Flurazepam Hydrochloride Capsules.

Fluspirilene *(BAN, USAN, rINN)*

Fluspirileenl; Fluspirilen; Fluspirilenas; Fluspirilène; Fluspirileno; Fluspirilenum; McN-JR-6218; R-6218; Флуспирилен
8-[4,4-Bis(4-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.
$C_{29}H_{31}F_2N_3O$=475.6
CAS — 1841-19-6.
ATC — N05AG01.
ATC Vet — QN05AG01.
UNII — C5QA4GLR9M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fluspirilene). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. Protect from light.

Profile

Fluspirilene is a diphenylbutylpiperidine antipsychotic and has general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.2). It is less likely to cause sedation. Fluspirilene has been given by deep intramuscular injection for the treatment of psychoses including schizophrenia (below). A usual initial dose is up to 2 mg weekly by deep intramuscular injection, increased according to response. Usual maintenance doses have ranged from 1 to 10 mg weekly although higher doses have been used in exceptional cases.

Adverse effects. References.

1. McCreadie RG, *et al.* Probable toxic necrosis after prolonged fluspirilene administration. *BMJ* 1979; 1: 523–4.

Schizophrenia. A systematic review[1] found that evidence to support the use of depot fluspirilene over oral chlorpromazine or other depot antipsychotics in the treatment of schizophrenia (p. 1031.3) was lacking.

1. Abhijnhan A, *et al.* Depot fluspirilene for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imap; *Belg.*: Imap; *Ger.*: Fluspi†; Imap; *Neth.*: Imap.

Flutoprazepam *(rINN)*

Flutoprazépam; Flutoprazepamum; KB-509; Флуторпразепам.
7-Chloro-1-(cyclopropylmethyl)-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.
$C_{19}H_{16}ClFN_2O$=342.8
CAS — 25967-29-7.
UNII — 2GHY1101MM.

Profile

Flutoprazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given for the short-term treatment of anxiety disorders (p. 1028.1) and insomnia (p. 1033.2). Typical oral doses are 2 to 4 mg once or twice daily; in the elderly, the maximum daily dose should be 4 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Restas.

Gepirone Hydrochloride *(USAN, rINNM)*

BMY-13805-1; Gepirona, hidrocloruro de; Gépirone, Chlorhydrate de; Gepironi Hydrochloridum; Hidrocloruro de gepirona; MJ-13805-1; Org-33062 (gepirone); Гепирона Гидрохлорид.
3,3-Dimethyl-*N*-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]glutarimide hydrochloride.
$C_{19}H_{29}N_5O_2.HCl$=395.9
CAS — 83928-76-1 (gepirone); 83928-66-9 (gepirone hydrochloride).

ATC — N06AX19.
ATC Vet — QN06AX19.
UNII — 80C9L8EP6V.

NOTE. The names Ariza and Variza have been used as trade marks for gepirone.

Profile

Gepirone is structurally related to buspirone (p. 1042.1). It has been investigated as the hydrochloride for the treatment of depression and anxiety disorders.

Action. Gepirone is a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the 5-HT_{1A} subtype. For reference to the actions and potential uses of such drugs, see Buspirone, p. 1042.2.

References.

1. Feiger AD, *et al.* Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. *J Clin Psychiatry* 2003; 64: 243–9.
2. Robinson DS, *et al.* A review of the efficacy and tolerability of immediate-release and extended-release formulations of gepirone. *Clin Ther* 2003; 25: 1618–33.
3. Amsterdam JD, *et al.* Sustained efficacy of gepirone-IR in major depressive disorder: a double-blind placebo substitution trial. *J Psychiatr Res* 2004; 38: 259–65.
4. Alpert JE, *et al.* Gepirone extended-release treatment of anxious depression: evidence from a retrospective subgroup analysis in patients with major depressive disorder. *J Clin Psychiatry* 2004; 65: 1069–75.
5. Keller MB, *et al.* Relapse prevention with gepirone ER in outpatients with major depression. *J Clin Psychopharmacol* 2005; 25: 79–84.
6. Bielski RJ, *et al.* Gepirone extended-release in the treatment of adult outpatients with major depressive disorder: a double-blind, randomized, placebo-controlled, parallel-group study. *J Clin Psychiatry* 2008; 69: 571–7.

Halazepam *(BAN, USAN, rINN)*

Halatsepaami; Halazépam; Halazepamum; Sch-12041; Галазепам.

7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepin-2-one.

$C_{17}H_{12}ClF_3N_2O$=352.7

CAS — 23092-17-3.
ATC — N05BA13.
ATC Vet — QN05BA13.
UNII — 320YC168LF.

Profile

Halazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given for the short-term treatment of anxiety disorders (p. 1028.1) in usual oral doses of 20 to 40 mg every 6 to 8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Pacinone; *Spain*: Alapryl.

Haloperidol *(BAN, USAN, rINN)*

Aloperidolo; Halopéridol; Haloperidoli; Haloperidolis; Haloperidolum; McN-JR-1625; R-1625; Галоперидол.

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone.

$C_{21}H_{23}ClFNO_2$=375.9

CAS — 52-86-8.
ATC — N05AD01.
ATC Vet — QN05AD01.
UNII — J6292F8L3D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Haloperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol, in dichloromethane, and in methyl alcohol. Protect from light.

USP 36: (Haloperidol). A white to faintly yellowish amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 15 of chloroform, and 1 in 200 of ether. A saturated solution is neutral to litmus. Store in airtight containers. Protect from light.

Dilution. See Incompatibility, below.

Incompatibility. A precipitate formed after dilution of haloperidol (as the lactate) in sodium chloride 0.9% injection when the final haloperidol concentration was 1 mg/mL or higher.[1]

Undiluted haloperidol (5 mg/mL) injection has been reported to be incompatible with heparin sodium (diluted in sodium chloride 0.9% or glucose 5% injection),[2] sodium nitroprusside (diluted in glucose 5%),[1] cefmetazole sodium,[3] and diphenhydramine.[4] A mixture of equal volumes of sargramostim 10 micrograms/mL and haloperidol (as the lactate) 200 micrograms/mL resulted in a precipitate at 4 hours.[5]

1. Outman WR, Monolakis J. Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; 48: 1539–41.
2. Solomon DA, Nasinnyk KK. Compatibility of haloperidol lactate and heparin sodium. *Am J Hosp Pharm* 1982; 39: 843–4.
3. Hutchings SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; 53: 2185–8.
4. Ukhun IA. Compatibility of haloperidol and diphenhydramine in a hypodermic syringe. *Ann Pharmacother* 1995; 29: 1168–9.
5. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; 49: 402–6.

Stability. A combination of the stabilisers benzyl alcohol and vanillin could protect haloperidol from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilisation of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; 67: 169–75.

Haloperidol Decanoate *(BANM, USAN, rINNM)*

Decanoato de haloperidol; Halopéridol, Décanoate d'; Haloperidol, decanoato de; Haloperidoldecanoat; Haloperidoldekanoat; Haloperidol-dekanoát; Haloperidoli Decanoas; Haloperidolidekanoatti; Haloperidolio dekanoatas; R-13672; Галоперидола Деканоат.

$C_{31}H_{41}ClFNO_3$=530.1

CAS — 74050-97-8.
ATC — N05AD01.
ATC Vet — QN05AD01.
UNII — AC20PJ4101.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Haloperidol Decanoate). A white or almost white powder. It melts at about 42 degrees. Practically insoluble in water; very soluble in alcohol, in dichloromethane, and in methyl alcohol. Store at a temperature below 25 degrees. Protect from light.

USP 36: (Haloperidol Decanoate). A white or almost white powder. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Haloperidol is a butyrophenone with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It is an antipsychotic with actions most closely resembling those of phenothiazines with a piperazine side-chain.

Haloperidol is used in the treatment of various psychoses including schizophrenia (below) and mania (see Bipolar Disorder, p. 397.2), and in behaviour disturbances (p. 1030.2), in Tourette's syndrome and severe tics (p. 1078.1), in intractable hiccups (p. 1046.3), and in severe anxiety (p. 1028.1), including for the sedation of patients in intensive care (p. 1033.1) or palliative care. Haloperidol has also been used for its antiemetic effect in the management of nausea and vomiting of various causes (p. 1814.3).

Haloperidol is usually given orally or by injection as the base or intramuscularly as the long-acting decanoate ester. Some haloperidol preparations are prepared with the aid of lactic acid and may be stated to contain haloperidol lactate. Doses are expressed in terms of the equivalent amount of haloperidol. Haloperidol decanoate 141 mg is equivalent to about 100 mg of haloperidol. Dosages should be reduced in elderly or debilitated patients; a usual starting dose is half the normal adult dose. Doses at the lower end of the scale are also advised for adolescents; for details of doses in children, see below.

The usual initial *oral* dose for the treatment of **psychoses** and associated behavioural disorders is 0.5 to 5 mg two or three times daily. In severe or resistant psychoses up to 30 mg daily is recommended in the UK, whereas in the USA doses of up to 100 mg daily are allowed; doses above 100 mg daily have rarely been used. The dose should be reduced gradually according to response. Maintenance doses as low as 3 to 10 mg daily may be sufficient.

For the control of acute psychotic conditions, haloperidol may be given *intramuscularly* in doses of 2 to 10 mg; subsequent doses may be given hourly, until symptoms are controlled, although dosage intervals of 4 to 8 hours may be adequate, up to a maximum of 18 mg daily. For the emergency control of very severely disturbed patients, an initial intramuscular dose of no more than 18 mg is recommended. The *intravenous* route has also been used.

In patients already stabilised on an oral dose of haloperidol and requiring long-term therapy the long-acting decanoate ester may be given by *deep intramuscular* injection. The usual initial dose is the equivalent of 10 to 20 times the total daily oral dose of haloperidol, up to a maximum of 100 mg; if more than 100 mg is required for an initial dose the excess should be given after 3 to 7 days. Subsequent doses, usually given every 4 weeks, may be increased in steps of 50 mg to up to 300 mg or more, according to the patient's requirements, both dose and dose interval being adjusted as required.

In the management of **nausea and vomiting** haloperidol has been given in a dose of 1 to 2 mg by *intramuscular* injection. In palliative care haloperidol 1.5 mg may be given orally once or twice daily, increased if necessary to 5 to 10 mg daily given in divided doses; alternatively, it may be given by *subcutaneous* infusion (via a syringe driver) in doses of 2.5 to 10 mg over 24 hours. The *intravenous* route has also been used.

A starting *oral* dose of 0.5 to 1.5 mg three times daily has been suggested for the management of **Tourette's syndrome** and severe **tics.** Up to about 30 mg daily may be needed in Tourette's syndrome, although requirements vary considerably and the dose must be very carefully adjusted to obtain the optimum response; a maintenance dose of 4 mg daily is effective for most patients.

For intractable **hiccups** a suggested *oral* dose is 1.5 mg given 3 times daily adjusted according to response.

An *oral* dose of 500 micrograms twice daily has been used as adjunctive treatment in the short-term management of severe **anxiety disorders.**

In palliative care, haloperidol has been given in a dose of 2 mg *orally* or 2.5 mg by *subcutaneous* injection, repeated every 2 hours if required, for the treatment of **restlessness and confusion.** It may also be given as a subcutaneous infusion in a dose of 5 to 15 mg over 24 hours.

Administration in children. In the UK, for the treatment of **schizophrenia** and **behavioural disorders** in children, a total daily maintenance oral dose of haloperidol 25 to 50 micrograms/kg is given in 2 divided doses. In the USA, a higher dose range of 50 to 150 micrograms/kg daily is given orally to those aged 3 to 12 years and weighing between 15 to 40 kg. A maximum daily dose of 10 mg has been recommended in the UK but US licensed product information states that there is little evidence of behaviour improvement with daily doses of more than 6 mg.

Although unlicensed for the management of **nausea and vomiting** in palliative care, the *BNFC* suggests that infants and children aged 1 month to 12 years may be given 25 to 85 micrograms/kg of haloperidol over 24 hours by continuous subcutaneous infusion; older children may be given 1.5 to 5 mg over 24 hours or an oral dose of 1.5 mg at night increased to 1.5 mg (maximum of 5 mg) twice daily if necessary. The intravenous route has also been used.

In the UK, for the management of **Tourette's syndrome** and severe **tics**, children may be given oral maintenance doses of up to 10 mg daily of haloperidol. Alternatively, the *BNFC* suggests that those aged 5 to 12 years may be given an oral dose of 12.5 to 25 micrograms/kg twice daily, adjusted according to response; older children may be given 1.5 mg three times daily. In the USA, oral doses of 50 to 75 micrograms/kg daily are given to those aged 3 to 12 years and weighing between 15 to 40 kg.

In palliative care, the *BNFC* suggests an oral dose of haloperidol 10 to 20 micrograms/kg every 8 to 12 hours for the treatment of **restlessness and confusion.**

Ballism. Dopamine-blocking antipsychotics such as haloperidol may sometimes be needed for the management of patients with ballism (p. 1029.3) when symptoms are severe.

Chorea. For a discussion of the management of various choreas, including mention of the use of haloperidol, see p. 1029.3.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to other drugs. However, they often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p. 1049.2).

Schizophrenia. Systematic reviews[1,2] of the use of haloperidol for schizophrenia (p. 1031.3) concluded that it appears to be of similar efficacy to chlorpromazine although it is associated with a high incidence of extrapyramidal adverse effects. An earlier systematic review[3] considered that the limited evidence did not indicate any advantages of giving haloperidol in doses greater than 7.5 mg daily to patients with uncomplicated acute schizophrenia.

1. Joy CB, *et al.* Haloperidol versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 19/03/08).
2. Leucht C, *et al.* Haloperidol versus chlorpromazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).

3. Waraich PS, *et al.* Haloperidol dose for the acute phase of schizophrenia. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2002 (accessed 19/03/08).

Sneezing. Intractable sneezing in a patient was controlled by haloperidol given in doses of up to 5 mg twice daily.[1] Symptoms recurred when treatment was stopped after 5 weeks but responded again to 5 mg three times daily. On gradual reduction of dosage over 6 months the patient had no recurrence and had remained symptom-free after 6 months without medication.

1. Davison K. Pharmacological treatment for intractable sneezing. *BMJ* 1982; **284**: 1163–4.

Stuttering. Stuttering (stammering) is a disorder that affects the fluency of speech. Developmental stuttering usually occurs in early childhood and is more common in boys than girls. While stuttering may cease in some children after only a few months, it may become a chronic condition in others. Stuttering that starts during adulthood is rarer and may be the result of a neurological insult. It should also be remembered that stuttering may be drug induced. While stuttering may be greatly improved with intensive speech training the efficacy of other forms of management such as hypnosis, psychotherapy, counselling, and drug therapy has been largely unconvincing.[1] Many drugs have been used to treat stuttering; however, a review of the literature[2] indicated that there were few adequate studies of their efficacy. Haloperidol was considered to be the most well studied drug and its efficacy had been shown by several double-blind placebo-controlled studies. Most patients needed to continue taking haloperidol to maintain improvement but few did so because of its adverse effects. Double-blind studies have on the whole failed to confirm reports of benefit for drugs such as beta blockers and calcium-channel blockers although isolated patients may have marked improvement. Other drugs that have been studied and which might be of benefit include clomipramine,[3] SSRIs,[4] and atypical antipsychotics[4] such as olanzapine and risperidone; formoterol, local anaesthetics, and injections of botulinum toxin have also been tried.

1. Andrews G, *et al.* Stuttering. *JAMA* 1988; **260**: 1445.
2. Brady JP, *et al.* The pharmacology of stuttering: a critical review. *Am J Psychiatry* 1991; **148**: 1309–16.
3. Gordon CT, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56**: 238–42.
4. Costa D, Kroll R. Stuttering: an update for physicians. *Can Med Assoc J* 2000; **162**: 1849–55.

Taste disorders. For reference to the use of haloperidol in the treatment of taste disorders, see Chlorpromazine, p. 1047.2.

Tourette's syndrome. Many patients with Tourette's syndrome (p. 1030.1) do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide are most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. However, superiority of either drug in terms of efficacy or adverse effects has not been clearly shown.[1,2] Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to be as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al.* Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; **46**: 722–30.
2. Sallee FR, *et al.* Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; **154**: 1057–62.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Haloperidol is less likely to cause sedation, hypotension, or antimuscarinic effects, but is associated with a higher incidence of extrapyramidal effects. Haloperidol should be used with great care in children and adolescents as they may be at increased risk of severe dystonic reactions; patients with hyperthyroidism may also be at increased risk. The risk of QT prolongation and/or ventricular arrhythmias may be increased with high doses or with parenteral use of haloperidol, particularly intravenous administration.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of haloperidol by mothers during breast feeding may be of concern, since there have been reports of decline in developmental scores in breast-fed infants. Licensed product information also reports that there have been isolated cases of extrapyramidal effects in breast-fed infants.

The concentration of haloperidol in breast milk of one mother given a mean daily dose of about 30 mg for 6 days was reported to be 5 nanograms/mL; on day 12 the concentration 9 hours after a 12-mg dose was 2 nanograms/mL.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. (Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Stewart RB, *et al.* Haloperidol excretion in human milk. *Am J Psychiatry* 1980; **137**: 849–50.

Convulsions. For mention of haloperidol as one of the antipsychotics suitable for patients at risk of seizures, see p. 1047.3.

Effects on the liver. Liver dysfunction with jaundice and eosinophilia developed in a 15-year-old male 4 weeks after starting haloperidol and benzatropine mesilate.[1] The drugs were stopped 2 weeks later but some symptoms lasted for 28 months. The reaction was suggestive of a drug-induced hypersensitivity reaction and haloperidol was the most likely cause. Haloperidol-induced liver injury was considered to be rare.

1. Dincsoy HP, Saelinger DA. Haloperidol-Induced chronic cholestatic liver disease. *Gastroenterology* 1982; **83**: 694–700.

Overdosage. Symptoms of haloperidol overdosage in children have ranged from the expected, such as drowsiness, restlessness, confusion, marked extrapyramidal symptoms, and hypothermia,[1,2] to unexpected reactions such as bradycardia (possibly secondary to hypothermia)[1] and an episode of severe, delayed hypertension.[3]

Torsade de pointes has followed overdosage in adults (for references, see Effects on the Cardiovascular System under Chlorpromazine, p. 1047.3).

1. Scialli JVK, Thornton WE. Toxic reactions from a haloperidol overdose in two children: thermal and cardiac manifestations. *JAMA* 1978; **239**: 48–9.
2. Sinaniotis CA, *et al.* Acute haloperidol poisoning in children. *J Pediatr* 1978; **93**: 1038–9.
3. Cummingham DG, Challapalli M. Hypertension in acute haloperidol poisoning. *J Pediatr* 1979; **95**: 489–90.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies haloperidol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Retroperitoneal fibrosis. Obstructive uropathy was noted in a 45-year-old woman given haloperidol 5 to 15 mg daily for 8 years.[1] Benzatropine was also taken during that time, and in the previous 5 years she had taken chlorpromazine and fluphenazine. Retroperitoneal fibrosis was diagnosed and was tentatively associated with long-term antipsychotic therapy.

1. Jeffries JJ, *et al.* Retroperitoneal fibrosis and haloperidol. *Am J Psychiatry* 1982; **139**: 1524–5.

Toxic encephalopathy. Possible toxic encephalopathy after use of high intravenous doses of haloperidol has been reported.[1] The patient, who had a history of bipolar disorder and cerebrovascular accident, had been given increasing intravenous doses of haloperidol (up to 270 mg daily) to control post-surgical agitation. The encephalopathy had resolved 8 days after stopping haloperidol.

1. Maxa JL, *et al.* Possible toxic encephalopathy following high-dose intravenous haloperidol. *Ann Pharmacother* 1997; **31**: 736–7.

Interactions

As for Chlorpromazine, p. 1051.3. The metabolism of haloperidol is mediated by several routes including the cytochrome P450 system, particularly the isoenzymes CYP3A4 and CYP2D6. Therefore, there is the potential for interactions between haloperidol and other drugs that induce, inhibit, or act as a substrate for these isoenzymes, resulting in altered haloperidol concentrations; it may be necessary to amend the dosage of haloperidol when given with such drugs. Haloperidol itself is also an inhibitor of CYP2D6 and may increase the plasma concentrations of tricyclic antidepressants by inhibiting their metabolism.

Haloperidol must be used with extreme caution in patients receiving lithium; an encephalopathic syndrome has been reported after their use together (see p. 431.3).

Pharmacokinetics

Haloperidol is readily absorbed from the gastrointestinal tract after oral use. It is metabolised in the liver and is excreted in the urine and, via the bile, in the faeces; there is evidence of enterohepatic recycling. Owing to first-pass metabolism in the liver, plasma concentrations after oral doses are lower than those after intramuscular injection. Moreover, there is wide intersubject variation in plasma concentrations of haloperidol. In practice, however, no strong correlation has been found between plasma concentrations of haloperidol and its therapeutic effect. Routes of metabolism of haloperidol include oxidative *N*-dealkylation, particularly via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, glucuronidation, and reduction of the ketone group to form an alcohol known as reduced haloperidol. Metabolites are ultimately conjugated with glycine. Haloperidol has been reported to have a plasma elimination half-life ranging from about 12 to 38 hours after oral doses. Haloperidol is about 92% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Haloperidol is distributed into breast milk.

The decanoate ester of haloperidol is very slowly absorbed from the injection site and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to haloperidol.

References.

1. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. *Clin Pharmacokinet* 1999 **37**: 435–56.

Metabolites. The clinical significance of the reduced metabolite of haloperidol has been much debated.[1,2] Its activity appears to be substantially less than that of the parent drug but there is some evidence for re-oxidation of reduced haloperidol to haloperidol.[1-3] Some studies suggest that nonresponders to haloperidol have elevated ratios of reduced haloperidol to haloperidol in the plasma, although other workers have reported contrary findings.[2] Pyridinium metabolites resulting from oxidation of haloperidol have been detected in the urine and there is concern that they may be neurotoxic in a manner similar to MPTP (see Parkinsonism, p. 889.1), a compound which can induce irreversible parkinsonism.[4]

1. Sramek JJ, *et al.* Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22**: 373–80.
2. Froemming JS, *et al.* Pharmacokinetics of haloperidol. *Clin Pharmacokinet* 1989; **17**: 396–423.
3. Chakraborty BS, *et al.* Interconversion between haloperidol and reduced haloperidol in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37**: 45–8.
4. Eyles DW, *et al.* Quantitative analysis of two pyridinium metabolites of haloperidol in patients with schizophrenia. *Clin Pharmacol Ther* 1994; **56**: 512–20.

Therapeutic drug monitoring. Measurement of concentrations of haloperidol or reduced haloperidol in scalp hair has been suggested as a useful means of monitoring compliance.[1,2] Evidence for the existence of any relationship between plasma concentrations of haloperidol and therapeutic effect in schizophrenia has been discussed.[3]

1. Uematsu T, *et al.* Human scalp hair as evidence of individual dosage history of haloperidol: method and retrospective study. *Eur J Clin Pharmacol* 1989; **37**: 239–44.
2. Matsuno H, *et al.* The measurement of haloperidol and reduced haloperidol in hair as an index of dosage history. *Br J Clin Pharmacol* 1990; **29**: 187–94.
3. Ulrich S, *et al.* The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. *Clin Pharmacokinet* 1998; **34**: 227–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Enabran†; Halopidol; Halozen; Limerix; Neupram; *Austral.*: Haldol; Serenace; *Austria*: Haldol; *Belg.*: Haldol; *Braz.*: Decan Haloper; Haldol; Halo; Haloper; Loperidol†; Uni Haloper; *Canad.*: Novo-Peridol; *Chile*: Alternus; Haldol; *China*: Haridol-D (哈力多-D); *Denm.*: Serenase; *Fin.*: Serenase; *Fr.*: Haldol; *Ger.*: Haldol; Haloper; *Gr.*: Alased; Aloperidin; Ovocterol; Sevium; *Hong Kong*: Haldol; Serenace; *India*: Benzydol-P; Brain-Rest; Cizoren; Depidol; Dolcin; Gendol; Haldol; Halidace; Halidol; Halobid; Halopace; Halopidol; Haloton; Hexidol; Larenase; Lodol; Mindol; Opreso; Serenace; *Indon.*: Dores; Govotil; Haldol; Lodomer; Serenace; *Irl.*: Haldol; Serenace; *Israel*: Haldol; Haloper; Pericate; Peridor†; *Ital.*: Haldol; Serenase; *Malaysia*: Manace; Mapress; *Mex*: Haldol; Haloperil; Hispadol; Kepsidol; Pulsit; Trenpe; *Neth*: Haldol; *Norw.*: Haldol; *NZ*: Haldol; Serenace; *Philipp.*: Haldol; Seredol; Serenace; *Pol.*: Decaldol; *Port.*: Haldol; *Rus.*: Haloper (Галопер)†; Senorm (Сенорм); *S.Afr.*: Serenace; *Singapore*: Haloxen; Manace; Serenace; *Swed.*: Haldol; *Switz.*: Haldol; *Thai.*: H-Tab; Haldol†; Halo-P; Halomed; Halopol; Haricon; Haridol; Perida†; Polyhadon; *Turk.*: Leptol; Norodol; Sedaperido; *UK*: Dozic; Haldol; Serenace; *USA*: Haldol; *Venez.*: Haldol; Tiplac.

Multi-ingredient Preparations. *India*: Cizoren Plus; Combidol; Halotex; Hexidol Forte; Hexidol Kit; Hexidol Plus; Manodol; Mindol Forte; Mindol Plus.

Pharmacopoeial Preparations

BP 2014: Haloperidol Capsules; Haloperidol Injection; Haloperidol Oral Solution; Haloperidol Tablets; Strong Haloperidol Oral Solution;
USP 36: Haloperidol Injection; Haloperidol Oral Solution; Haloperidol Tablets.

Haloxazolam (rINN)

Haloxazolamum; Галоксазолам.
10-Bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

$C_{17}H_{14}BrFN_2O_2$=377.2
CAS — 59128-97-1.
UNII — M448L2V8XP.

Pharmacopoeias. In *Jpn.*

Profile

Haloxazolam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given as a hypnotic in the short-term management of insomnia (p. 1033.2) in usual oral doses of 5 or 10 mg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Somelin.

Iloperidone *(BAN, USAN, rINN)*

HP-873; ILO-522; Iloperidona; Iloperidone; Iloperidonum; Илоперидон.
4′-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3′-methoxyacetophenone.
$C_{24}H_{27}FN_2O_4$=426.5
CAS — 133454-47-4.
UNII — VPO7KJ050N.

Uses and Administration

Iloperidone is a benzisoxazole atypical antipsychotic reported to be an antagonist at dopamine D_2, serotonin (5-HT_2), and adrenergic (α_1 and α_2) receptors. It is given orally for the treatment of schizophrenia (p. 1031.3) in an initial dose of 1 mg twice daily, increased to 2, 4, 6, 8, 10, and 12 mg twice daily on days 2 to 7, respectively, to the target dose range of 6 to 12 mg twice daily. If therapy has been interrupted for more than 3 days, the dose of iloperidone should be re-titrated.

The usual dose should be reduced by one-half in those who are also taking potent inhibitors of the cytochrome P450 isoenzymes CYP2D6 (such as fluoxetine or paroxetine) or CYP3A4 (such as clarithromycin or ketoconazole), and in poor metabolisers of CYP2D6 substrates.

References.

1. Potkin SG, *et al.* Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. *J Clin Psychopharmacol* 2008; **28** (suppl 1): S4–S11.
2. Kane JM, *et al.* Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol* 2008; **28** (suppl 1): S29–S35.
3. Scott LJ. Iloperidone: in schizophrenia. *CNS Drugs* 2009; **23**: 867–80.
4. Caccia S, *et al.* New atypical antipsychotics for schizophrenia: iloperidone. *Drug Des Devel Ther* 2010; **4**: 33–48.
5. Citrome L. Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. *Expert Opin Drug Metab Toxicol* 2010; **6**: 1551–64.
6. Arif SA, Mitchell MM. Iloperidone: a new drug for the treatment of schizophrenia. *Am J Health-Syst Pharm* 2011; **68**: 301–8.

Adverse Effects, Treatment, and Precautions

Although iloperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with iloperidone are dizziness, somnolence, fatigue, dry mouth, nasal congestion, and weight gain. Other common adverse effects include nausea, diarrhoea, extrapyramidal effects, and arthralgia. Priapism, leucopenia, and hyperprolactinaemia resulting in gynaecomastia and galactorrhoea occur rarely.

Iloperidone has been associated with QT prolongation; it should be stopped in those with persistent QT_c measurements of more than 500 milliseconds. Orthostatic hypotension associated with dizziness, tachycardia, and syncope has also been frequently reported. Iloperidone should be used with caution in patients with cardiovascular or cerebrovascular disease, or with conditions that may predispose to hypotension; in addition, it should be avoided in those with a history of arrhythmias or other conditions that may increase the risk of QT prolongation including bradycardia, recent myocardial infarction, or electrolyte disturbances such as hypokalaemia and hypomagnesaemia. Certain drugs may also increase the risk (see Interactions, below). Baseline serum potassium and magnesium screening should be performed before starting iloperidone therapy in patients who are at risk of significant electrolyte disturbances and periodically monitored thereafter.

Seizures have been noted with iloperidone and it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

Use in patients with hepatic impairment is not recommended due to a lack of data.

Iloperidone may affect the performance of skilled tasks such as driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics and recommendations for monitoring are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with dementia is also discussed in further detail under Risperidone, p. 1105.1.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by iloperidone. Iloperidone is also an α_1-adrenergic antagonist and may enhance the effects of some antihypertensives. There may be an increased risk of QT prolongation when iloperidone is given with other drugs that are known to cause this effect.

The metabolism of iloperidone is mediated by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Use with drugs that inhibit these isoenzymes can increase plasma concentrations of iloperidone and a dose reduction of iloperidone is recommended.

Pharmacokinetics

Iloperidone is well absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within 2 to 4 hours. It is about 95% bound to serum proteins. Iloperidone is metabolised in the liver mainly by carbonyl reduction, hydroxylation (mediated by the cytochrome P450 isoenzyme CYP2D6 and subject to genetic polymorphism), and *O*-demethylation (mediated by CYP3A4). Excretion is mainly in the urine and, to a lesser extent, in the faeces.

Distribution into milk has been found in studies in *rats.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel:* Fanapt; *USA:* Fanapt.

Ketazolam *(BAN, USAN, rINN)*

Ketatsolaami; Kétazolam; Ketazolamum; U-28774; Кетазолам.
11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-*d*][1,4]benzodiazepine-4,7(6*H*)-dione.
$C_{20}H_{17}ClN_2O_3$=368.8
CAS — 27223-35-4.
ATC — N05BA10.
ATC Vet — QN05BA10.
UNII — 92A214MD7Y.

Profile

Ketazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given in the short-term treatment of anxiety (p. 1028.1) in usual oral doses of 15 to 60 mg daily, either in divided doses or as a single dose at night. Reduced doses may be required in elderly or debilitated patients.

References.

1. Angelini G, *et al.* Ketazolam, a new long-acting benzodiazepine, in the treatment of anxious patients: a multicenter study of 2,056 patients. *Curr Ther Res* 1989; **45**: 294–304.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ansieten; *Chile*: Ansietil; Sedatival; *Ital.*: Anseren; *Port.*: Unakalm; *S.Afr.*: Solatran†; *Spain*: Marcen†; Sedotime; *Switz.*: Solatran.

Levomepromazine *(BAN, USAN, rINN)*

CL-36467; CL-39743; Levomepromatsiini; Levomepromazin; Levomepromazina; Lévomépromazine; Levomepromazinum; Methotrimeprazine; RP-7044; SKF-5116; XP-03; Левомепромазин.
(-)-*NN*-Dimethyl-3-(2-methoxyphenothiazin-10-yl)-2-methylpropylamine; 3-(2-Methoxyphenothiazin-10-yl)-2-methylpropyldimethylamine.
$C_{19}H_{24}N_2OS$=328.5
CAS — 60-99-1.
ATC — N05AA02.
ATC Vet — QN05AA02.
UNII — 9G0LAW7ATQ.

Pharmacopoeias. In *US.*

USP 36: (Methotrimeprazine). A fine white, practically odourless, crystalline powder. Soluble 1 in 10 of water, of alcohol, and of methyl alcohol, and 1 in 2 of chloroform; freely soluble in ether; sparingly soluble in alcohol at 25 degrees but freely soluble in boiling alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Levomepromazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levomepromazina; Levomepromatsiinihydrokloridi; Levomepromazin hydrochlorid; Levomepromazina, hidrocloruro de; Lévomépromazine, chlorhydrate de; Levomepromazin-hidroklorid; Levomepromazinhydrochlorid; Levomepromazinhydroklorid; Levomepromazini Hydrochloridum; Levomepromazino hidrochloridas; Lewomepromazyny chlorowodorek; Methotrimeprazine Hydrochloride; Левомепромазина Гидрохлорид.
$C_{19}H_{24}N_2OS$,HCl=364.9
CAS — 4185-80-2; 1236-99-3.
ATC — N05AA02.
ATC Vet — QN05AA02.
UNII — 42B81Y2586.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Levomepromazine Hydrochloride). A white or very slightly yellow, slightly hygroscopic crystalline powder. It deteriorates on exposure to air and light. Freely soluble in water and in alcohol. Store in airtight containers. Protect from light.

Incompatibility. Levomepromazine hydrochloride is reported to be incompatible with alkaline solutions.

Levomepromazine Maleate

(BANM, USAN, rINNM)

Levomepromatsiinimaleaatti; Levomepromazin maleinát; Levomepromazina, maleato de; Lévomépromazine, Maléate de; Levomepromazini maleas; Levomepromazinmaleat; Levomepromazin-maleát; Levomepromazino maleatas; Lewomepromazyny maleinian; Maleato de levomepromazina; Methotrimeprazine Hydrogen Maleate; Methotrimeprazine Maleate; Левомепромазина Малеат.
$C_{19}H_{24}N_2OS$,$C_4H_4O_4$=444.5
CAS — 7104-38-3.
ATC — N05AA02.
ATC Vet — QN05AA02.
UNII — 5KN5Y9V01K.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Levomepromazine Maleate). A white or slightly yellowish crystalline powder. It deteriorates when exposed to air and light. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. The supernatant of a 2% dispersion in water has a pH of 3.5 to 5.5. Protect from light.

Uses and Administration

Levomepromazine is a phenothiazine with pharmacological activity similar to that of both chlorpromazine (p. 1045.3) and promethazine (p. 638.3). It has antihistaminic actions (p. 610.1) as well as CNS effects resembling those of chlorpromazine. It is also reported to have analgesic and antiemetic activity. It is used in the treatment of various psychoses including schizophrenia (p. 1031.3), as an analgesic for moderate to severe pain, and for premedication (see Anaesthesia, p. 1899.1). It is also used in palliative care for the control of symptoms such as restlessness, agitation, pain (p. 1080.1), and nausea and vomiting (p. 1814.3).

Levomepromazine is also used in veterinary medicine.

Levomepromazine is given orally as the maleate or the hydrochloride, or by injection as the hydrochloride. In the UK, doses such as those given below are expressed in terms of the appropriate salt. However, in some countries, the dose of levomepromazine may be expressed in terms of the

base. The embonate has also been used. Care is required in elderly patients because of the risk of severe hypotension; if levomepromazine is given to such patients reduced doses may be necessary.

The usual initial oral dose of levomepromazine maleate for the treatment of **schizophrenia** is 25 to 50 mg daily; the daily dosage is usually divided into 3 portions with a larger portion taken at night. Doses of 100 to 200 mg have been given to non-ambulant patients increased gradually to 1 g daily if necessary.

When used in **palliative care** for the management of severe terminal **pain** and associated **restlessness and agitation**, levomepromazine hydrochloride 12.5 to 25 mg may be given intramuscularly, or by intravenous injection after dilution with an equal volume of sodium chloride 0.9% injection; in cases of severe agitation, up to 50 mg may be given every 6 to 8 hours. Alternatively it may be given, suitably diluted with sodium chloride 0.9% injection, by continuous subcutaneous infusion via a syringe driver; doses range from a total of 25 to 200 mg daily. Patients given large initial doses should remain in bed. If oral therapy is more convenient, levomepromazine maleate may be given orally in a dose of 12.5 to 50 mg every 4 to 8 hours. Although it is licensed for such use either as monotherapy or adjunctive therapy, the *BNF* recommends that it should be reserved as an adjunct to opioid analgesia in patients with severe pain unresponsive to other measures. The *BNF* also suggests an oral dose of levomepromazine maleate 6 to 50 mg daily given as a single dose or in 2 divided doses for the management of **nausea and vomiting** where first-line antiemetics have proved inadequate. Alternatively, it may be given by continuous subcutaneous infusion (as above) in doses ranging from a total of 5 to 25 mg daily; however, sedation can limit the dose.

For details of doses in children, see below.

Levomepromazine hydrochloride given parenterally has been used in some countries for the control of acute pain, as a **premedicant**, and for postoperative analgesia. In some countries levomepromazine is also licensed for use as an **anxiolytic** and **sedative**, and in the management of other types of pain, including **labour pain**.

Administration in children. Levomepromazine may be used in children for the treatment of various psychoses including schizophrenia although they are very susceptible to its hypotensive and sedative effects: licensed product information suggests giving a 10-year-old an oral dose of 12.5 to 25 mg of the maleate daily in divided doses; a dose of 37.5 mg daily should not be exceeded.

Experience with parenteral use of levomepromazine hydrochloride in children is limited but the *BNFC* suggests a dose of 100 to 400 micrograms/kg given over 24 hours by continuous intravenous or subcutaneous infusion for those aged 1 month to 12 years in the management of nausea and vomiting in palliative care; older children may be given the usual adult dose (see p. 1079.3). It has also been used in the treatment of pain and associated restlessness and confusion in palliative care in a dose of 0.35 to 3 mg/kg given over 24 hours by continuous subcutaneous infusion for those aged 1 to 12 years; older children may be given the usual adult dose (see above).

Pain. As levomepromazine appears to possess intrinsic analgesic activity in addition to its antiemetic and antipsychotic actions it has been used for the symptomatic control of restlessness and vomiting and as an adjunct to opioid analgesics in pain control (see Choice of Analgesic, p. 4.2) in terminally ill patients.

References.
1. Oliver DJ. The use of methotrimeprazine in terminal care. *Br J Clin Pract* 1985; 39: 339–40.
2. Patt RB, *et al.* The neuroleptics as adjuvant analgesics. *J Pain Symptom Manage* 1994; 9: 446–53.
3. O'Neill J, Fountain A. Levomepromazine (methotrimeprazine) and the last 48 hours. *Hosp Med* 1999; 60: 564–7.
4. Skinner J, Skinner A. Levomepromazine for nausea and vomiting in advanced cancer. *Hosp Med* 1999; 60: 568–70.

HEADACHE. Levomepromazine is one of those phenothiazines (see p. 1046.3) that has been effective[1] in relieving the pain of severe migraine attacks.

1. Stiell IG, *et al.* Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; 20: 1201–5.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2, although it may be more sedating. See also Adverse Effects of Antihistamines, p. 613.1.

Levomepromazine may cause severe orthostatic hypotension, and patients taking large initial doses, patients over 50 years of age, or those given injections, should be lying down. Children are very susceptible to the hypotensive and sedative effects of levomepromazine.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levomepromazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Antidepressants. Although *MAOIs* have been used with phenothiazines without untoward effects, the use of levomepromazine with MAOIs should probably be avoided as this combination has been implicated in 2 fatalities.[1,2]

1. Barsa JA, Saunders JC. A comparative study of tranylcypromine and pargyline. *Psychopharmacologia* 1964; 6: 295–8.
2. McQueen EG. New Zealand committee on adverse drug reactions: fourteenth annual report 1979. *N Z Med J* 1980; 91: 226–9.

Pharmacokinetics

In a study involving 5 psychiatric patients peak plasma concentrations of levomepromazine were noted 1 to 4 hours after oral doses and 30 to 90 minutes after injection into the gluteal muscle.[1] About 50% of an oral dose reached the systemic circulation. Although the metabolite levomepromazine sulfoxide could not be detected after a single intramuscular injection, it was found in concentrations higher than unmetabolised levomepromazine after single and multiple oral dosage, both substances reaching a steady state in the plasma within 7 days of starting multiple-dose oral therapy. Fluctuations in plasma concentration during multiple-dose oral therapy indicated that until the correlation between acute adverse effects and peak plasma concentration of levomepromazine had been further studied the total daily dose should be divided into 2 or 3 portions when larger oral doses of levomepromazine are used.

1. Dahl SG. Pharmacokinetics of methotrimeprazine after single and multiple doses. *Clin Pharmacol Ther* 1976; 19: 435–42.

Half-life. In 8 psychiatric patients given levomepromazine 50 to 350 mg daily the plasma half-life showed wide variation, from 16.5 to 77.8 hours, and did not correlate with the dose given.[1]

1. Dahl SG, *et al.* Pharmacokinetics and relative bioavailability of levomepromazine after repeated administration of tablets and syrup. *Eur J Clin Pharmacol* 1977; 11: 305–310.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Detenler; Levolam; Nozinan; Sunonix; Togrel; *Austria*: Nozinan; *Belg.*: Nozinan; *Braz.*: Levozine; Meprozin; Neozine; *Canad.*: Apo-Methoprazine; Novo Meprazine; Nozinan; *Chile*: Sinogan; *Cz.*: Tisercin; *Denm.*: Nozinan; *Fin.*: Levozin; Nozinan†; *Fr.*: Nozinan; *Ger.*: Levium†; Neurocil; *Gr.*: No-Calm; Nozinan; Sinogan; *Hung.*: Tisercin; *Irl.*: Nozinan; *Israel*: Methozane†; Nozinan; Ronexine; *Ital.*: Nozinan; *Mex.*: Levocina; Sinogan; *Neth.*: Nozinan; *Norw.*: Nozinan; *NZ*: Nozinan; *Philipp.*: Nozinan; *Pol.*: Tisercin; *Port.*: Nozinan; *Rus.*: Tisercin (Тизерцин); *Spain*: Sinogan; *Swed.*: Nozinan; *Switz.*: Nozinan; *UK*: Levinan; Nozinan; *Ukr.*: Tisercin (Тизерцин); *Venez.*: Sinogan.

Pharmacopoeial Preparations
BP 2014: Levomepromazine Injection; Levomepromazine Tablets;
USP 36: Methotrimeprazine Injection.

Loprazolam Mesilate *(BANM, rINNM)*

HR-158; Loprazolam, Mésilate de; Loprazolam, mesilato de; Loprazolam Mesylate; Loprazolam Methanesulphonate; Loprazolami Mesilas; Mesilato de loprazolam; RU-31158; Лопразолама Мезилат.

6-(2-Chlorophenyl)-2,4-dihydro-2-(4-methylpiperazin-1-ylmethylene)-8-nitroimidazo[1,2-*a*][1,4]benzodiazepin-1-one methanesulphonate monohydrate.

$C_{23}H_{21}ClN_6O_3.CH_4O_3S.H_2O$=579.0

CAS — 61197-73-7 (loprazolam); 70111-54-5 (anhydrous loprazolam mesilate).
ATC — N05CD11.
ATC Vet — QN05CD11.
UNII — VKF8383J65.

Pharmacopoeias. In *Br.*

BP 2014: (Loprazolam Mesilate). A yellow crystalline powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether.

Uses and Administration

Loprazolam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is usually used as a hypnotic in the short-term management of insomnia (p. 1033.2). Loprazolam is given as the mesilate but doses are expressed in terms of the base: loprazolam mesilate 1.25 mg is equivalent to about 1 mg of loprazolam. Usual oral doses are equivalent to 1 mg of loprazolam at night; this may be increased to up to 2 mg if necessary. A starting dose of 500 micrograms increased to a maximum of 1 mg may be appropriate for elderly or debilitated patients.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 0.5 to 1 mg of loprazolam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

References.
1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; 16: 337–64.
2. Dorling MC, Hindmarch I. Pharmacokinetic profile of loprazolam in 12 young and 12 elderly healthy volunteers. *Drugs Exp Clin Res* 2001; 27: 151–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dormonoct; *Belg.*: Dormonoct; *Fr.*: Havlane; *Neth.*: Dormonoct; *Port.*: Dormonoct; *S.Afr.*: Dormonoct; *Spain*: Somnovit.

Pharmacopoeial Preparations
BP 2014: Loprazolam Tablets.

Lorazepam *(BAN, USAN, rINN)*

Loratsepaami; Lorazepám; Lorazépam; Lorazepamas; Lorazepamum; Wy-4036; Лоразепам.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1,4-benzodiazepin-2-one.

$C_{15}H_{10}Cl_2N_2O_2$=321.2

CAS — 846-49-1.
ATC — N05BA06.
ATC Vet — QN05BA06.
UNII — O26FZP769L.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of lorazepam:

Benzo; Somnios.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Lorazepam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; sparingly or slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Lorazepam). A white or practically white, practically odourless powder. Insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Visual incompatibility has been noted with lorazepam and sargramostim[1] or aztreonam.[2]

1. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; 49: 402–6.
2. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; 52: 1086–90.

Solubility. The solubility of lorazepam in fluids for intravenous use (water, glucose injection, lactated Ringer's injection, and sodium chloride injection) was greatest in glucose injection 5% at 62 micrograms/mL and lowest in sodium chloride injection 0.9% at 27 micrograms/mL;[1] these differences in solubility appeared to be pH related. Commercial injections are reported to contain polyethylene glycol in propylene glycol to overcome this poor solubility. However, precipitation has been noted[2] in solutions prepared by dilution of lorazepam injection with sodium chloride injection 0.9% to a concentration of 500 micrograms/mL. One group of workers[3] have reported that they had overcome such problems of precipitation by using glucose injection 5% as a diluent and by avoiding final concentrations of lorazepam between 80 micrograms/mL and 1 mg/mL. It was suggested that the propylene glycol in the mixture might account for the unusual concentration effect. Such recommendations have been adopted by another group[4] although they saw that precipitation occurred if a formulation of lorazepam containing

4 mg/mL was used to prepare the injection; no precipitation was noted when a formulation containing 2 mg/mL was used. The group also commented that a US manufacturer of lorazepam injection advised that admixtures should be prepared with the 2 mg/mL formulation only.

1. Newton DW, *et al.* Lorazepam solubility in and sorption from intravenous admixture solutions. *Am J Hosp Pharm* 1983; 40: 424–7.
2. Boullata JI, *et al.* Precipitation of lorazepam infusion. *Ann Pharmacother* 1996; 30: 1037–8.
3. Volles DF, *et al.* More on usability of lorazepam admixtures for continuous infusion. *Am J Health-Syst Pharm* 1996; 53: 2753–4.
4. Levanda M. Noticeable difference in admixtures prepared from lorazepam 2 and 4 mg/mL. *Am J Health-Syst Pharm* 1998; 55: 2305.

Sorption. Significant loss of lorazepam has been reported from solutions stored in PVC[1] or polypropylene[2] giving equipment; polyolefin[3-5] or glass[6] equipment appears to be more suitable.

1. Hoey LL, *et al.* Lorazepam stability in parenteral solutions for continuous intravenous administration. *Ann Pharmacother* 1996; 30: 343–6.
2. Stiles ML, *et al.* Stability of deferoxamine mesylate, floxuridine, fluorouracil, hydromorphone hydrochloride, lorazepam, and midazolam hydrochloride in polypropylene infusion-pump syringes. *Am J Health-Syst Pharm* 1996; 53: 1583–8.
3. Trissel LA, Pearson SD. Storage of lorazepam in three injectable solutions in polyvinyl chloride and polyolefin bags. *Am J Hosp Pharm* 1994; 51: 368–72.
4. Norenberg JP, *et al.* Stability of lorazepam in 0.9% sodium chloride stored in polyolefin bags. *Am J Health-Syst Pharm* 2004; 61: 1039–41.
5. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; 63: 2379–82.
6. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47: 369–73.

Uses and Administration

Lorazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term treatment of anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1), as a hypnotic in the short-term management of insomnia (p. 1033.2), and as an anticonvulsant particularly in the management of status epilepticus (p. 510.2). Lorazepam has a prolonged antiepileptic action and may be the preferred initial treatment in status epilepticus if intravenous access is available. It is also used for its sedative and amnestic properties in premedication and as an adjunct in regimens for the control of nausea and vomiting associated with cancer chemotherapy (below).

Lorazepam is usually given orally or by injection as the base although the pivalate is available for oral use in some countries. Sublingual tablets are used in some countries in doses similar to those for standard tablets. The intramuscular route is usually only used when oral or intravenous dosage is not possible. Injections should usually be diluted before use; intravenous injections should be given at a rate of not more than 2 mg/minute into a large vein. Lorazepam should be given in reduced dosage to elderly or debilitated patients; half the usual adult dose, or less, may be sufficient.

The usual oral dose of lorazepam for the treatment of **anxiety disorders** is 1 to 6 mg daily in 2 or 3 divided doses with the largest dose taken at night; up to 10 mg daily has been given. A dose of 25 to 30 micrograms/kg may be given by injection every 6 hours for acute anxiety. Lorazepam has also been used for **panic disorder**. A suggested oral dose in the *BNF* is 3 to 5 mg daily. For acute attacks, parenteral lorazepam may be given; the *BNF* suggests a dose of 25 to 30 micrograms/kg (usual range 1.5 to 2.5 mg) repeated every 6 hours if necessary. A single oral dose of 1 to 4 mg at bedtime may be given for **insomnia** associated with anxiety. However, the MHRA in the UK advises against the use of oral daily doses of lorazepam above 4 mg for anxiety and phobia, and 2 mg for insomnia.

For **premedication** an oral dose of 2 to 3 mg may be given the night before the operation followed by a further dose of 2 to 4 mg given 1 to 2 hours before the operation. Lorazepam may also be given parenterally for premedication; UK licensed product information recommends that a dose of 50 micrograms/kg may be given 30 to 45 minutes before the operation if given intravenously or 1 to 1½ hours before if given intramuscularly. Similar regimens are also used in other countries; US licensed product information suggests a maximum dose of 4 mg when given intravenously or intramuscularly.

In the management of **status epilepticus** 4 mg may be given as a single intravenous dose; this may be repeated once after 10 to 15 minutes if seizures continue or recur. The *BNF* suggests that this dose may also be given for febrile **convulsions** and convulsions due to poisoning.

For details of doses in children, see below.

In patients receiving modestly emetogenic chemotherapy, lorazepam 1 to 2 mg orally may be added to antiemetic therapy with domperidone or metoclopramide, for the prophylaxis of **nausea and vomiting**. The addition of lorazepam may be helpful in the prevention of anticipatory symptoms because of its anxiolytic, sedative, and amnestic effects.

Administration in children. For **premedication** in children, the *BNFC* suggests that 50 to 100 micrograms/kg (maximum of 4 mg) of lorazepam may be given orally at least 1 hour before surgery to those aged 1 month to 12 years; older children may be given 1 to 4 mg. The same dose may be given the night before in addition to, or to replace, the dose before the operation. The *BNFC* also suggests that 50 to 100 micrograms/kg (maximum of 4 mg) may be given by slow intravenous injection, over 3 to 5 minutes (maximum rate of 50 micrograms/kg over 3 minutes), 30 to 45 minutes before the operation to those aged 1 month to 18 years. In the UK, oral lorazepam is licensed for use in children aged 5 years and over and parenteral preparations are licensed in those aged 12 years and over *when used as a premedicant*.

In the management of **status epilepticus** UK licensed product information recommends a single intravenous dose of 2 mg. Alternatively, the *BNFC* suggests that neonates and children up to 12 years old may be given 100 micrograms/kg (maximum of 4 mg) as a single dose by slow intravenous injection; this may be repeated once after 10 minutes if necessary. Older children may be given the usual adult dose (see above). The *BNFC* also recommends these doses for febrile convulsions and convulsions due to poisoning.

Catatonia. Lorazepam has been tried[1,2] with some success in the treatment of catatonia.

1. Manjunatha N, *et al.* Idiopathic recurrent catatonia needs maintenance lorazepam: case report and review. *Aust N Z J Psychiatry* 2007; 41: 625–7.
2. Seethalakshmi R, *et al.* Catatonic syndrome: importance of detection and treatment with lorazepam. *Ann Clin Psychiatry* 2008; 20: 5–8.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders and the value of benzodiazepines, see p. 1030.2.

References.

1. Bieniek SA, *et al.* A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; 18: 57–62.
2. Alexander J, *et al.* Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting: pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. *Br J Psychiatry* 2004; 185: 63–9.

Nausea and vomiting. Lorazepam is used as an adjunct[1,2] for the control of nausea and vomiting associated with cancer chemotherapy (p. 1814.3).

1. Malik IA, *et al.* Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin: a prospective randomized trial. *Am J Clin Oncol* 1995; 18: 170–5.
2. Bleicher J, *et al.* Lorazepam, diphenhydramine, and haloperidol transdermal gel for rescue from chemotherapy-induced nausea/vomiting: results of two pilot trials. *J Support Oncol* 2008; 6: 27–32.

Premedication and sedation. Lorazepam is used as a premedicant (see Anaesthesia, p. 1899.1) and as a sedative for therapeutic and investigative procedures such as dental treatment (p. 1032.2) and endoscopy (p. 1032.3), and also in intensive care (p. 1033.1).

References.

1. Maltais F, *et al.* A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest* 1996; 109: 1195–8.

Substance dependence. Lorazepam has been used in the management of symptoms of alcohol withdrawal (p. 1735.1).

References.

1. D'Onofrio G, *et al.* Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; 340: 915–19.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 500 micrograms of lorazepam may be considered equivalent to about 5 mg of diazepam.

Withdrawal symptoms. In a prospective open-label study[1] of 29 children, withdrawal symptoms occurred in 7 after stopping lorazepam, which had been used for sedation during mechanical ventilation; the dose of lorazepam had been tapered over 6 days before stopping treatment.

1. Dominguez KD, *et al.* Withdrawal from lorazepam in critically ill children. *Ann Pharmacother* 2006; 40: 1035–9.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. Pain and a sensation of burning have occurred after injection of lorazepam.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of lorazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Free lorazepam concentrations in the breast milk of 4 mothers ranged from 8 to 9 nanograms/mL four hours after receiving a 3.5-mg oral dose.[2] This represented about 15 to 26% of the concentration in plasma, and was probably sufficiently low to cause no adverse effects in breast-fed infants.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth* 1985; 57: 1042–3.

Effects on the blood. A case of pancytopenia associated with oral lorazepam was reported[1] in 1988; only 5 instances of thrombocytopenia and none of leucopenia had been reported to the UK CSM or the UK manufacturers over the previous 13 years.

1. El-Sayed S, Symonds RP. Lorazepam induced pancytopenia. *BMJ* 1988; 296: 1332.

Effects on fluid and electrolyte homoeostasis. Inappropriate secretion of antidiuretic hormone related to ingestion of lorazepam was considered to be the cause of hyponatraemia in an 81-year-old woman.[1]

1. Engel WR, Grau A. Inappropriate secretion of antidiuretic hormone associated with lorazepam. *BMJ* 1988; 297: 858.

Effects on the nervous system. For reference to extrapyramidal disorders associated with use of lorazepam, see Diazepam, p. 1066.1.

The elderly. For discussion of the need for reduced dosage of benzodiazepines in elderly patients, see Diazepam, p. 1067.2.

Formulation. Some parenteral formulations of lorazepam contain benzyl alcohol, polyethylene glycol, and propylene glycol. Benzyl alcohol may cause 'gasping syndrome' in neonates (see p. 1741.1) and should be avoided in infants and children up to 3 years old. Polyethylene glycol and propylene glycol have also been reported to cause toxicity (see p. 2205.3) particularly in patients with renal or hepatic impairment and in children.

Hepatic impairment. Lorazepam is contra-indicated in severe hepatic impairment; patients with mild to moderate impairment may require reduced doses. Although the elimination half-life of lorazepam was increased in 13 patients with alcoholic cirrhosis compared with 11 control subjects, this was not associated with an impairment in systemic plasma clearance.[1] With the exception of a modest decrease in the extent of plasma protein binding, acute viral hepatitis had no effect on the disposition kinetics of lorazepam.

1. Kraus JW, *et al.* Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; 24: 411–19.

Local reactions. Of 40 patients given a single intravenous dose of lorazepam 4 mg three had local thrombosis 2 to 3 days later and 6 had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution].

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; 2: 1384–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lorazepam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Lorazepam is readily absorbed from the gastrointestinal tract after oral doses, with a bioavailability of about 90%; peak plasma concentrations occur about 2 hours after an oral dose. The absorption profile after intramuscular injection is similar to that after oral dosage.

Lorazepam is about 85% bound to plasma proteins. It crosses the blood-brain barrier and the placenta; it is also distributed into breast milk. Lorazepam is metabolised in the liver to the inactive glucuronide, and excreted in the urine. The elimination half-life has been reported to range from about 10 to 20 hours.

References.

1. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; 6: 89–105.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; 57: 135–43.

3. Swart EL, *et al.* Population pharmacokinetics of lorazepam and midazolam and their metabolites in intensive care patients on continuous venovenous hemofiltration. *Am J Kidney Dis* 2005; 45: 360–71.
4. Chung JY, *et al.* Effect of the UGT2B15 genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. *Clin Pharmacol Ther* 2005; 77: 486–94.
5. de Wit M, *et al.* Lorazepam concentrations, pharmacokinetics and pharmacodynamics in a cohort of mechanically ventilated ICU patients. *Int J Clin Pharmacol Ther* 2006; 44: 466–73.

Children. References[1,2] to the pharmacokinetics of lorazepam in children.

1. Relling MV, *et al.* Lorazepam pharmacodynamics and pharmacokinetics in children. *J Pediatr* 1989; 114: 641–6.
2. Muchohi SN, *et al.* Pharmacokinetics and clinical efficacy of lorazepam in children with severe malaria and convulsions. *Br J Clin Pharmacol* 2008; 65: 12–21.

NEONATES. References[1-3] to slow elimination of lorazepam by neonates.

1. Cummings AJ, Whitelaw AGL. A study of conjugation and drug elimination in the human neonate. *Br J Clin Pharmacol* 1981; 12: 511–15.
2. McDermott CA, *et al.* Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992; 120: 479–83.
3. Reiter PD, Stiles AD. Lorazepam toxicity in a premature infant. *Ann Pharmacother* 1993; 27: 727–9.

Distribution. Evidence suggests that lorazepam undergoes enterohepatic recirculation with possible first-pass metabolism.[1]

1. Herman RJ, *et al.* Disposition of lorazepam in human beings: enterohepatic recirculation and first-pass effect. *Clin Pharmacol Ther* 1989; 46: 18–25.

CNS. In a study involving 6 healthy subjects, peak plasma-lorazepam concentrations were reached 5 minutes after the end of a one-minute intravenous injection.[1] CNS effects, as measured by EEG activity, were not maximal until 30 minutes after injection; they declined to baseline values slowly over 5 to 8 hours in a similar manner to plasma concentrations. In contrast, CNS effects of diazepam were maximal immediately after the injection. They also declined more rapidly than lorazepam, but again in a similar way to plasma concentrations. Studies in *mice* suggested that the slow onset of action of lorazepam that has been reported by some is at least partly explained by a delay in passage from systemic blood into brain tissue.

1. Greenblatt DJ, *et al.* Kinetic and dynamic study of intravenous lorazepam: comparison with intravenous diazepam. *J Pharmacol Exp Ther* 1989; 250: 134–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aplacasse; Calmatron; Emotival; Kalmalin; Lorezan; Lyovial; Microzepam; Nervistop; Sidenar; Trapax; ***Austral.***: Ativan; ***Austria***: Merlit; Temesta; ***Belg.***: Doclorazet†; Lauracalm†; Lorazemed†; Lorazetop; Loridem; Optisedine; Serenase; Temesta; ***Braz.***: Ansirax; Lorapan; Lorax; Lorazefast; Max-Pax; Mesmerin; ***Canad.***: Ativan; Novo-Lorazem; Nu-Loraz; ***Chile***: Abinol; Amparax; ***China***: Jia Pu Le (佳普乐); Le La An (乐拉安); Lora (罗拉); ***Denm.***: Orfidal; Temesta; ***Fin.***: Temesta; ***Fr.***: Temesta; ***Ger.***: Tavor; Tolid; ***Gr.***: Aripax; Ativan; Cicletan; Dorm; Modium; Nevrogamma; Nifalin; Novhepar; Proneurit; Tavor; Titus; Trankilium; ***Hong Kong***: LAtiwen†; Lorans; Lorivan; Silence; ***India***: Almazine; Anxipose; Atipam; Ativan; C-Van; Calmese; L-Pam; L-Zepam; Larpose; Lopez; Lora; Loracalm; Loraz; Lorcin; Lorel; Loripam; Lorivan; Lorpik; Lorvan; Oratric; Orazep; ***Indon.***: Ativan†; Merlopam; Renaquil; ***Irl.***: Ativan; ***Israel***: Lorivan; ***Ital.***: Control; Loralin; Lorans; Slipirem†; Tavor; Zeloram; ***Malaysia***: Ativan†; Lorans; ***Mex.***: Ativan; Sinestron; ***Neth.***: Temesta; ***NZ***: Ativan; ***Pol.***: Lorafen; ***Port.***: Ansilor; Lorenin; Lorsedal; Rialam; ***Rus.***: Lorafen (Лорафен); ***S.Afr.***: Ativan; Tranqipam; ***Singapore***: Ativan†; Lorans; ***Spain***: Donix; Idalprem†; Orfidal; Placinoral; ***Swed.***: Temesta; ***Switz.***: Lorasifar; Sedazin; Temesta; ***Thai.***: Anta; Anxira; Hawkcopax; Kemora; Lizavan; Lonza; Lora-P; Lora; Loramed; Lorapam†; Lorapine; Loravan; Lorazep; Lorazin; Lozepam; Ora; Razepam; Tranavan; Vemed; Zora; ***Turk.***: Ativan; ***UK***: Ativan; ***USA***: Ativan; ***Venez.***: Ativan.

Multi-ingredient Preparations. ***Switz.***: Somnium.

Pharmacopoeial Preparations
BP 2014: Lorazepam Injection; Lorazepam Tablets;
USP 36: Lorazepam Injection; Lorazepam Oral Concentrate; Lorazepam Tablets.

Lormetazepam *(BAN, USAN, rINN)*

Lormetatsepaami; Lormétazépam; Lormetazepamum; Wy-4082; Лометазепам.

(*RS*)-7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-1,4-benzodiazepin-2-one.

$C_{16}H_{12}Cl_2N_2O_2$=335.2

CAS — 848-75-9.

ATC — N05CD06.

ATC Vet — QN05CD06.

UNII — GU56C842ZA.

Pharmacopoeias. In *Br.*

BP 2014: (Lormetazepam). A white crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

Uses and Administration

Lormetazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is mainly used as a hypnotic in the short-term management of insomnia (p. 1033.2) in usual oral doses of 0.5 to 1.5 mg at night. A dose of 500 micrograms is recommended for elderly or debilitated patients. Lormetazepam is also used in some countries for premedication.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 0.5 to 1 mg of lormetazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Lormetazepam is rapidly absorbed from the gastrointestinal tract after oral doses, with a bioavailability of about 80%; peak plasma concentrations are reported to occur about 1.5 hours after an oral dose. Binding to plasma proteins is extensive. It is metabolised in the liver to the inactive glucuronide, and excreted in the urine. The terminal half-life is reported to be about 11 hours.

A brief review of the pharmacokinetics of lormetazepam.[1]

1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; 8: 233–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Noctamid; ***Belg.***: Doclormeta†; Loramet; Loranka; Lormetamed†; Metatop; Noctacalm†; Noctamid; Octonox†; Sedaben; Stilaze; ***Chile***: Nocton; ***Denm.***: Pronoctan; ***Fr.***: Noctamide; ***Ger.***: Ergocalm; Loretam; Noctamid; ***Gr.***: Loramet; Noctamid; ***Irl.***: Noctamid; ***Ital.***: Axilium; Ipnolor; Luzul; Mexylor; Minias; ***Neth.***: Noctamid; ***NZ***: Noctamid; ***Pol.***: Noctofer; ***S.Afr.***: Loramet; Noctamid; ***Spain***: Aldosomnil; Loramet; Noctamid; ***Switz.***: Loramet; Noctamid; ***Thai.***: Loramet.

Pharmacopoeial Preparations
BP 2014: Lormetazepam Tablets.

Loxapine *(BAN, USAN, rINN)*

CL-62362; Loksapiini; Loxapin; Loxapina; Loxapinum; Oxilapine; SUM-3170; Локсапин.

2-Chloro-11-(4-methylpiperazin-1-yl)dibenz[*b,f*][1,4]oxazepine.

$C_{18}H_{18}ClN_3O$=327.8

CAS — 1977-10-2.

ATC — N05AH01.

ATC Vet — QN05AH01.

UNII — LER583670J.

Loxapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de loxapina; Loxapina, hidrocloruro de; Loxapine, Chlorhydrate de; Loxapini Hydrochloridum; Локсапина Гидрохлорид.

$C_{18}H_{18}ClN_3O$,HCl=364.3

ATC — N05AH01.

ATC Vet — QN05AH01.

UNII — 376MYL4MAL.

Loxapine Succinate *(BANM, USAN, rINNM)*

CL-71563; Loxapina, succinato de; Loxapine, Succinate de; Loxapini Succinas; Succinato de loxapina; Локсапина Сукцинат.

$C_{18}H_{18}ClN_3O$,$C_4H_5O_4$=446.0

CAS — 27833-64-3.

ATC — N05AH01.

ATC Vet — QN05AH01.

UNII — X59SG0MRYU.

Pharmacopoeias. In *US.*

USP 36: (Loxapine Succinate). A white to yellowish, odourless, crystalline powder. Store in airtight containers.

Uses and Administration

Loxapine is a dibenzoxazepine with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It is used for the treatment of psychoses including schizophrenia (below) and for acute agitation associated with bipolar disorder (p. 397.2) or schizophrenia.

In the treatment of psychoses including schizophrenia, loxapine is given orally as the succinate and by intramuscular injection as the base. Doses are expressed in terms of the base; loxapine succinate 34 mg is equivalent to about 25 mg of loxapine. The usual oral dose is 20 to 50 mg daily initially, in 2 divided doses, increased according to response over the next 7 to 10 days to 60 to 100 mg daily or more, in 2 to 4 divided doses; the maximum recommended dose is 250 mg daily. Maintenance doses are usually in the range of 20 to 60 mg daily, in divided doses. For the control of acute conditions it is given by intramuscular injection in daily doses of up to 300 mg in 2 or 3 divided doses. Reduced dosage may be required in elderly patients.

Loxapine is also given by oral inhalation (as the base) in the treatment of acute agitation associated with bipolar disorder or schizophrenia; the usual dose is 10 mg once in a 24-hour period.

Loxapine has also been given orally and by intramuscular injection as the hydrochloride.

Disturbed behaviour. The use of inhaled loxapine in the treatment of acute agitation in patients with bipolar disorder[1] or schizophrenia[2,3] has been studied.

For a discussion of the use and limitations of antipsychotics such as loxapine in patients with disturbed behaviour, see p. 1030.2.

1. Kwentus J, *et al.* Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipolar Disord* 2012; 14: 31–40.
2. Lesem MD, *et al.* Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. *Br J Psychiatry* 2011; 198: 51–8.
3. Allen MH, *et al.* Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2011; 72: 1313–21.

Schizophrenia. A brief review of loxapine[1] found no conclusive evidence that it was particularly effective in patients with paranoid schizophrenia (p. 1031.3). A subsequent systematic review considered that the limited evidence did not indicate a clear difference in its effects from other antipsychotics.[2]

1. Anonymous. Clozapine and loxapine for schizophrenia. *Drug Ther Bull* 1991; 29: 41–2.
2. Chakrabarti A, *et al.* Loxapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 19/03/08).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Other adverse effects reported include nausea and vomiting, seborrhoea, dyspnoea, ptosis, headache, paraesthesia, facial flush, weight gain or loss, and polydipsia. Dysgeusia and throat irritation have been reported following the oral inhalation of loxapine.

Loxapine oral inhalation can cause bronchospasm which could lead to respiratory distress and respiratory arrest. It is contra-indicated in patients with a history of asthma, bronchospasm, or acute respiratory symptoms. All patients should be monitored for breathing difficulties at least every 15 minutes for a minimum of one hour following an oral inhalation of loxapine.

Abuse. There has been a report of 3 cases of loxapine succinate abuse.[1]

1. Sperry L, *et al.* Loxapine abuse. *N Engl J Med* 1984; 310: 598.

Effects on carbohydrate metabolism. Reversible nonketotic hyperglycaemia, coma, and delirium developed in a patient receiving loxapine 150 mg daily in addition to lithium therapy.[1] Symptoms improved on stopping loxapine, but subsequently recurred when the patient was given amoxapine. The causative agent may have been 7-hydroxyamoxapine, a common metabolite of both amoxapine and loxapine.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; 44: 347–8.

Mania. A patient, initially diagnosed as having schizophrenia, developed manic symptoms after receiving loxapine.[1] The diagnosis was revised to schizoaffective disorder but it was suspected that loxapine had a role in the emergence of the affective symptoms. As loxapine shares common metabolites with the antidepressant amoxapine it was suggested that an antidepressant effect might have precipitated the manic symptoms.

1. Gojer JAC. Possible manic side-effects of loxapine. *Can J Psychiatry* 1992; 37: 669–70.

Overdosage. An 8-year-old child was treated with activated charcoal within 30 minutes of being given 375 mg of loxapine by accident.[1] The child became drowsy and was asleep but arousable 1 hour after ingestion. The degree of sedation appeared to peak after 3.75 hours and the child was discharged about 20 hours after ingestion.

1. Tarricone NW. Loxitane overdose. *Pediatrics* 1998; 101: 496.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Loxapine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 2 hours. It is rapidly absorbed following oral inhalation with peak plasma concentrations occurring within 2 minutes. It is very rapidly and extensively metabolised and there is evidence for a first-pass effect. It is mainly excreted in the urine, in the form of its conjugated metabolites, with smaller amounts appearing in the faeces as unconjugated metabolites; a substantial proportion of a dose is excreted in the first 24 hours. The terminal elimination half-life ranges from 6 to 8 hours. The major metabolites of loxapine are the active 7- and 8-hydroxyloxapine, which are conjugated to the glucuronide or sulfate; other metabolites include hydroxyloxapine-*N*-oxide, loxapine-*N*-oxide, and hydroxydesmethylloxapine (hydroxyamoxapine). Loxapine is widely distributed and is 96.6% bound to plasma proteins. It is thought, on the basis of *animal* studies, to cross the placenta and be distributed into breast milk.

References.

1. Spyker DA, *et al.* Pharmacokinetics of loxapine following inhalation of a thermally generated aerosol in healthy volunteers. *J Clin Pharmacol* 2010; 50: 169–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Loxapac; *Fr.*: Loxapac; *Gr.*: Loxapac; *India*: Loxapac; *USA*: Adasuve; Loxitane.

Pharmacopoeial Preparations
USP 36: Loxapine Capsules.

Lurasidone Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lurasidona; Lurasidone, Chlorhydrate de; Lurasidoni Hydrochloridum; SM-13496 (lurasidone or lurasidone hydrochloride); SMP-13496 (lurasidone); Луразидона Гидрохлорид.

(3a*R*,4*S*,7*R*,7*S*)-2-{(1*R*,2*R*)-2-[(1,2-Benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride.

$C_{28}H_{36}N_4O_2S$,HCl=529.1

CAS — 367514-87-2 (lurasidone); 367514-88-3 (lurasidone hydrochloride).

ATC — N05AE05.

ATC Vet — QN05AE05.

UNII — O0P4I5851I.

Profile

Lurasidone hydrochloride is an atypical antipsychotic reported to be an antagonist at dopamine D_2, serotonin 5-HT_{2A} and 5-HT_7, and adrenergic α_{2A} and α_{2C} receptors, and a partial agonist at serotonin 5-HT_{1A} receptors. It may be given orally for the treatment of schizophrenia (p. 1031.3) in an initial dose of 40 mg once daily with food; the maximum recommended daily dose is 160 mg.

Lurasidone hydrochloride is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and those who are also taking moderate CYP3A4 inhibitors (such as diltiazem) should be given an initial dose of 20 mg daily; the maximum recommended daily dose is 80 mg. Use with potent CYP3A4 inhibitors (such as ketoconazole) or inducers (such as rifampicin) is not recommended.

Reduced doses are recommended in patients with hepatic or renal impairment, see Administration in Hepatic and Renal Impairment, below.

References.

1. Nakamura M, *et al.* Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; 70: 829–36.
2. Meyer JM, *et al.* Lurasidone: a new drug in development for schizophrenia. *Expert Opin Invest Drugs* 2009; 18: 1715–26.

Administration in hepatic impairment. An initial oral dose of 20 mg daily of lurasidone is recommended for patients with moderate (Child-Pugh score of 7 to 9) or severe (Child-Pugh score of 10 to 15) hepatic impairment. The maximum recommended daily dose is 40 mg for those with severe impairment and 80 mg for moderate impairment.

Administration in renal impairment. An initial oral dose of 20 mg daily of lurasidone is recommended for patients with moderate (creatinine clearance [CC] of 30 to < 50 mL/min) or severe (CC of < 30 mL/min) renal impairment; the maximum recommended daily dose is 80 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Latuda; *Switz.*: Latuda; *USA*: Latuda.

Medazepam *(BAN, rINN)*

Medatsepaami; Médazépam; Medazepamum; Медазепам.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine.

$C_{16}H_{15}ClN_2$=270.8

CAS — 2898-12-6.

ATC — N05BA03.

ATC Vet — QN05BA03.

UNII — P0J3387W3S.

Pharmacopoeias. In *Jpn*.

Medazepam Hydrochloride *(USAN)*

Medazepam, hidrocloruro de; Ro-5-4556.

$C_{16}H_{15}ClN_2$,HCl=307.2

CAS — 2898-11-5.

ATC — N05BA03.

ATC Vet — QN05BA03.

UNII — ETM878JC9K.

Profile

Medazepam is a long-acting benzodiazepine with properties similar to those of diazepam (p. 1063.2). It has been given for the short-term treatment of anxiety disorders (p. 1028.1). A usual oral dose is 10 to 30 mg daily given in 2 or 3 divided doses, or as a single dose at night; a maximum of 60 mg daily may be given in severe conditions. Reduced doses should be given to elderly or debilitated patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Ansilan; *Ger.*: Rudotel; Rusedal; *Hung.*: Nobrium†; Rudotel; Rusedal†; *Pol.*: Rudotel; *Rus.*: Mezapam (Мезапам); Rudotel (Рудотель); *Thai.*: Celium; Medazine.

Multi-ingredient Preparations. *Ital.*: Debrum; *Spain*: Nobritol; *Turk.*: Tanko-Buskas†; Tranko-Buskas.

Medetomidine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de medetomidina; Medetomidinihydrokloridi; Medetomidina, hidrocloruro de; Médétomidine, Chlorhydrate de; Medetomidinhydroklorid; Medetomidini Hydrochloridum; MPV-785; Медетомидина Гидрохлорид.

(±)-4-[1-(2,3-Xylyl)ethyl]imidazole monohydrochloride.

$C_{13}H_{16}N_2$,HCl=236.7

CAS — 86347-15-1 (medetomidine hydrochloride); 86347-14-0 (medetomidine).

ATC Vet — QN05CM91.

UNII — 8H210P244U.

Profile

Medetomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Its *S*-enantiomer dexmedetomidine (p. 1063.1) is used as the hydrochloride for sedation in intensive care and in surgical and medical procedures.

Melperone Hydrochloride *(BANM, rINNM)*

FG-5111; Flubuperone Hydrochloride; Hidrocloruro de melperona; Melperon Hidroklorür; Melperona, hidrocloruro de; Melpérone, Chlorhydrate de; Melperoni Hydrochloridum; Methylperone Hydrochloride; Мелперона Гидрохлорид.

4′-Fluoro-4-(4-methylpiperidino)butyrophenone hydrochloride.

$C_{16}H_{22}FNO$,HCl=299.8

CAS — 3575-80-2 (melperone); 1622-79-3 (melperone hydrochloride).

ATC — N05AD03.

ATC Vet — QN05AD03.

UNII — 88G640374K.

Profile

Melperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given orally as the hydrochloride for the management of psychoses such as schizophrenia (below) and in disturbed behaviour (p. 1030.2); doses are expressed as the hydrochloride. A usual oral dose is up to 400 mg daily in divided doses. It has also been given intramuscularly in acute conditions.

Cardiac arrhythmias. Melperone has been reported to have class III electrophysiologic and antiarrhythmic activity[1,2] but its clinical use as an antiarrhythmic would be limited by a high incidence of adverse effects.[2] For a discussion of the cardiovascular effects of antipsychotics in general, see under Chlorpromazine, p. 1047.3.

1. Mogelvang JC, *et al.* Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; 208: 61–4.
2. Hui WKK, *et al.* Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; 15: 144–9.

Pharmacokinetics. References.

1. Köppel C, *et al.* Gas chromatographic-mass spectrometric study of urinary metabolism of melperone. *J Chromatogr Biomed Appl* 1988; 427: 144–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies melperone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Schizophrenia. References[1-3] to the use of melperone in schizophrenia (p. 1031.3). It has been suggested that melperone should be considered as an atypical antipsychotic in view of the low incidence of extrapyramidal effects associated with its use.

1. Meltzer HY, *et al.* Melperone in the treatment of neuroleptic-resistant schizophrenia. *Psychiatry Res* 2001; 105: 201–9.
2. Sumiyoshi T, *et al.* The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. *Schizophr Res* 2003; 59: 7–16.
3. Sumiyoshi T, *et al.* A comparison of two doses of melperone, an atypical antipsychotic drug, in the treatment of schizophrenia. *Schizophr Res* 2003; 62: 65–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Buronil; *Belg.*: Buronil; *Cz.*: Buronil; *Denm.*: Buronil; *Fin.*: Melpax†; *Ger.*: Eunerpan†; Mel-Puren†; Melneurin†; *Port.*: Bunil; *Swed.*: Buronil; *Turk.*: Buronon†.

Meprobamate *(BAN, rINN)*

Meprobamaatti; Meprobamat; Meprobamát; Meprobamatas; Méprobamate; Meprobamato; Meprobamatum; Meprotanum; Мепробамат.

2-Methyl-2-propyltrimethylene dicarbamate.

$C_9H_{18}N_2O_4$=218.3

CAS — 57-53-4.

ATC — N05BC01.

ATC Vet — QN05BC01.

UNII — 9I7LNY769Q.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of meprobamate:

Miltown; Mother's little helper; Uncle Miltie.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet*.

Ph. Eur. 8: (Meprobamate). A white or almost white, crystalline or amorphous powder. Slightly soluble in water; freely soluble in alcohol.

USP 36: (Meprobamate). A white powder having a characteristic odour. Slightly soluble in water; freely soluble in alcohol and in acetone; practically insoluble or insoluble in ether. Store in airtight containers.

Uses and Administration

Meprobamate is a carbamate with hypnotic, sedative, and some muscle relaxant properties, although in therapeutic doses its sedative effect rather than a direct action may be responsible for muscle relaxation. It has been used in the short-term treatment of anxiety disorders (p. 1028.1) and also for the short-term management of insomnia (p. 1033.2) but has largely been superseded by other drugs (see also under Adverse Effects and Treatment, p. 1084.1). Meprobamate has sometimes been used, alone or with an analgesic, in the management of muscle spasm (p. 2014.1) and painful musculoskeletal disorders but such use is no longer considered appropriate.

The usual anxiolytic dose is 400 mg orally three or four times daily to a maximum of 2.4 g daily. In elderly patients, no more than half the usual adult dose has been suggested.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects and Treatment

Drowsiness is the most frequent adverse effect of meprobamate. Other effects include nausea, vomiting, diarrhoea, paraesthesia, weakness, and CNS effects such as headache, paradoxical excitement, dizziness, ataxia, and disturbances of vision. There may be hypotension, tachycardia, and cardiac arrhythmias. Hypersensitivity reactions occur occasionally. These may be limited to rashes, urticaria, and purpura or may be more severe with angioedema, bronchospasm, or anuria. Erythema multiforme or Stevens-Johnson syndrome, and exfoliative or bullous dermatitis have been reported.

Blood disorders including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and aplastic anaemia have occasionally been reported.

Overdosage with meprobamate produces symptoms similar to those of barbiturate overdosage (see Amobarbital, p. 1038.1), and is managed similarly; activated charcoal, given orally or by nasogastric tube, may be considered in patients who present within 1 hour of ingesting a toxic dose (more than 60 mg/kg in adults) or after any amount in a child.

In 2012, the European Medicines Agency reviewed[1,2] available data on the safety and efficacy of oral meprobamate-containing preparations and concluded that the risks, particularly of serious CNS adverse effects, outweigh any benefits. The gradual withdrawal of such preparations from the EU market was recommended, although they amy remain available in other countries.

1. EMEA. Press release: European Medicines Agency recommends suspension of marketing authorisations for meprobamate-containing medicines in the European Union—gradual withdrawal period of 15 months recommended (issued 20th January, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/01/WC500120728.pdf (accessed 08/08/13)
2. EMEA. Questions and answers on the suspension of the marketing authorisations for oral meprobamate-containing medicines (issued 30th March, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/meprobamate_107/WC500120737.pdf (accessed 08/08/13)

Overdosage. Two children aged 2 and 2.5 years recovered with conservative management alone after overdosage of meprobamate with bendroflumethiazide despite measured plasma-meprobamate concentrations of 170 and 158 micrograms/mL, respectively.[1] Although it had been recommended that haemoperfusion should be considered at plasma-meprobamate concentrations above 100 micrograms/mL, the authors considered that experience with adults suggested haemoperfusion should normally only be considered at plasma concentrations above 200 micrograms/mL.

A retrospective study[2] of 74 patients admitted to an intensive care unit for meprobamate poisoning found that 29 developed hypotension (mean meprobamate plasma concentration 106 micrograms/mL); no predictive factor for the development of hypotension was identified. However, in another study[3] of 59 cases of meprobamate poisoning, mean plasma concentrations of meprobamate measured on admittance were found to be correlated with the resulting coma according to the Glasgow Coma Scale (GCS):

- GCS group A: 111.05 micrograms/mL
- GCS group B: 80.77 micrograms/mL
- GCS group C: 62.6 micrograms/mL

The authors considered that the determination of meprobamate concentrations was essential to ensure the use of appropriate care.

1. Dennison J, *et al.* Meprobamate overdosage. *Hum Toxicol* 1985; 4: 215–17.
2. Charron C, *et al.* Incidence, causes and prognosis of hypotension related to meprobamate poisoning. *Intensive Care Med* 2005; 31: 1582–6.
3. Buire A-C, *et al.* Overdose of meprobamate: plasma concentration and Glasgow Coma Scale. *Br J Clin Pharmacol* 2009; 68: 126–7.

Precautions

Meprobamate is contra-indicated in patients with acute pulmonary insufficiency or respiratory depression. Meprobamate should be used with caution in patients with hepatic or renal impairment, depression, muscle weakness, and, as with all sedatives, in those with respiratory disease. Meprobamate should be given with care to elderly or debilitated patients. Meprobamate may induce seizures in those with a history of epilepsy.

Meprobamate may cause drowsiness; affected patients should not drive or operate machinery.

Breast feeding. Licensed product information states that the use of meprobamate should be avoided in breast feeding mothers as concentrations in milk may be up to four times those in maternal plasma and may cause drowsiness in the infant.

Pregnancy. Licensed product information states that meprobamate should be avoided during pregnancy, particularly during the first trimester, as some studies,[1] but not all,[2] have suggested an increased risk of congenital malformations associated with the use of anxiolytics (including meprobamate).

In a group of 107 women who had attempted suicide using large doses of meprobamate, there were 42 live births, 39 pregnancy terminations, and 24 miscarriages or early fetal losses;[3] 2 women were lost to follow up. Of the 42 live births, 34 mothers used other drugs in their suicide attempts, in particular, the benzodiazepine diazepam; the dose of meprobamate used for the suicide attempt by this group ranged from 1 g to 26 g, with a mean of 3.69 g. Congenital abnormalities were noted in 7 of the exposed children, but the incidence of abnormalities was not significantly different when compared with sibling controls. Neurological development was also comparable with sibling controls.

1. Milkovich L, van den Berg BJ. Effects of prenatal meprobamate and chlordiazepoxide hydrochloride on human embryonic and fetal development. *N Engl J Med* 1974; 291: 1268–71.
2. Hartz SC, *et al.* Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. *N Engl J Med* 1975; 292: 726–8.
3. Timmermann G, *et al.* A study of teratogenic and fetotoxic effects of large doses of meprobamate used for a suicide attempt by 42 pregnant women. *Toxicol Ind Health* 2008; 24: 97–107.

Interactions

The sedative effects of meprobamate are enhanced by CNS depressants including alcohol. Meprobamate is capable of inducing hepatic microsomal enzyme systems involved in drug metabolism: the metabolism of other drugs may be enhanced if given concurrently.

Pharmacokinetics

Meprobamate is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after ingestion. Meprobamate is widely distributed; plasma protein binding is about 20%. It is extensively metabolised in the liver and is excreted in the urine mainly as an inactive hydroxylated metabolite and its glucuronide conjugate. About 10% of a dose is excreted unchanged. Meprobamate has a half-life reported to range from about 6 to 17 hours, although this may be prolonged after chronic use.

It diffuses across the placenta and appears in breast milk at concentrations of up to 4 times those in the maternal plasma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Microbamat†; Miltaun†; ***Fr.***: Equanil†; ***Gr.***: Praol†; ***Hung.***: Andaxin†; ***Israel***: Mepro; ***Ital.***: Quanil†; ***S.Afr.***: Equanil; ***Switz.***: Meprodil†; ***Thai.***: Reinbamate.

Multi-ingredient Preparations. ***Canad.***: 282 MEP†; ***Chile***: Butartrol; ***Fin.***: Anervan†; Crampiton; ***Fr.***: Kaologeais†; Meproniz ine†; Precyclan†; ***Indon.***: Deparon†; ***Mex.***: Artrilan†; ***Norw.***: Anervan†; ***S.Afr.***: Adco-Payne; Adco-Synaleve; Antipyn Forte; Ban Pain†; Briscopyn†; Dynapayne; Equagesic†; Fevapar; Go-Pain; Medipyn; Megapyn; Meprogesic; Mepromol; Micro-Gesic†; Painagon; Painrite†; Pynmed; Salterpyn; Spectrapain Forte; Stilpanet; Stilpane; Stopayne; Supragesic; Tenston†; Tenston; Trinagesic; Vacudol Fortet; ***Turk.***: Danitrin Fort; ***UK***: Paxidal†; ***USA***: Equagesic.

Pharmacopoeial Preparations
USP 36: Meprobamate Oral Suspension; Meprobamate Tablets.

Mesoridazine *(BAN, USAN, rINN)*

Mesoridatsiini; Mesoridazin; Mesoridazina; Mésoridazine; Mesoridazinum; Mesuridazine; Mezoridazin; NC-123; TPS-23; Мезоридазин.

10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylsulphinyl)phenothiazine.

$C_{21}H_{26}N_2OS_2$=386.6

CAS — 5588-33-0.
ATC — N05AC03.
ATC Vet — QN05AC03.
UNII — SXE4NWM740.

Mesoridazine Besilate *(BANM, rINNM)*

Bencenosulfonato de mesoridazina; Besilato de mesoridazina; Mesoridazina, besilato de; Mesoridazine Benzenesulphonate; Mésoridazine, Bésilate de; Mesoridazine Besylate; Mesoridazini Besilas; Mesuridazine Benzenesulphonate; Мезоридазина Безилат.

$C_{21}H_{26}N_2OS_2.C_6H_6O_3S$=544.7

CAS — 32672-69-8 (mesoridazine besilate).
ATC — N05AC03.
ATC Vet — QN05AC03.
UNII — T4G21958J2.

Pharmacopoeias. In *US.*

USP 36: (Mesoridazine Besylate). A white to pale yellowish powder having not more than a faint odour. Soluble 1 in of water, 1 in 11 of alcohol, 1 in 3 of chloroform, and 1 in 6300 of ether; freely soluble in methyl alcohol. pH of freshly prepared 1 in 100 solution is between 4.2 and 5.7 Store in airtight containers. Protect from light.

Profile

Mesoridazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain and is a metabolite of thioridazine (p. 1110.2). Mesoridazine was usually given as the besilate orally or by intramuscular injection.

Mesoridazine has been shown to prolong the QT interval in a dose-related manner which increases the risk of life threatening arrhythmias such as torsade de pointes and sudden death; consequently its use in schizophrenia was restricted. (For further details see under Precautions of Thioridazine, p. 1111.1). Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential, and it is no longer available in many countries.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of mesoridazine on breast fed infants is unknown, its use by mothers during breastfeeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Lidanil.

Pharmacopoeial Preparations
USP 36: Mesoridazine Besylate Injection; Mesoridazine Besylate Oral Solution; Mesoridazine Besylate Tablets.

Methaqualone *(BAN, USAN, rINN)*

CI-705; CN-38703; Metacualona; Metakvalon; Metakvalonas; Metakvaloni; Methachalonum; Methakvalon; Methaqualon; Méthaqualone; Methaqualonum; QZ-2; R-148; TR-495; Метаквалон.

2-Methyl-3-*o*-tolylquinazolin-4-(3*H*)-one.

$C_{16}H_{14}N_2O$=250.3

CAS — 72-44-6 (methaqualone); 340-56-7 (methaqualone hydrochloride).
ATC — N05CM01.
ATC Vet — QN05CM01.
UNII — 7ZKH8MQW6T.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methaqualone:

300's; 712; 714; 714s; Bandits; Beiruts; Blou Bulle; Blue Balls; Blue bulls; Disco biscuits; Down and dirtys; Drunfos; Drunken Monkey; Ewings; Flamingos; Flowers; Fourstrokes; Fuckers; Genuines; Germans; Golfsticks; Gorilla Biscuits; Humbles; Joe Fridays; Knoppies; Lemmon 714; Lemmons; Lemons; Lennons; Lewds; Lizards; Loss-of-memory; Love drug; Lovers; Ludes; Luds; Lula; Magwheels; Mandies; No. 714; Pressouts; Pupumala; Q; Qua; Quaa; Quaalude; Quaaludes; Quaas; Quack; Quacks; Quad; Quads; Quas; Quay; Roar; Seven fourteen; Seven fourteens; Shiny Tops; Soaper; Soapers; Sopes; Sopor; Sopors; Sporos; Strawberries; Super Sopors; Supers; Supper; The love drug; Three hundreds; Vitamin Q; Wagon Wheels; Wallbangers; Whore pills.

Profile

Methaqualone is a quinazoline derivative with hypnotic and sedative properties. It has been given orally in the short-term management of insomnia but the use of methaqualone for this purpose is no longer considered appropriate. It has also been given with diphenhydramine for an enhanced effect.

Methaqualone has been withdrawn from the market in many countries because of problems with abuse.

Adverse effects and symptoms of overdosage are similar to those of barbiturates (see Amobarbital, p. 1038.1) although cardiac and respiratory depression reportedly occur less frequently.

Abuse. Although oral abuse of methaqualone has greatly declined in developed countries after the widespread withdrawal of the tablets, smoking of (usually illicitly manufactured) methaqualone, generally with cannabis and tobacco, is a major public health problem in South Africa, and some other parts of Africa and India. Although diazepam has been used to manage dependence, controlled studies to assess treatment efficacy are lacking.[1]

1. McCarthy G, *et al.* Treatment for methaqualone dependence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 11/05/06).

Mexazolam *(rINN)*

CS-386; Methylcloxazolam; Mexazolamum; Мексазолам.
10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-3-methyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.
$C_{18}H_{16}Cl_2N_2O_2$=363.2
CAS — 31868-18-5.
UNII — S596986237.

Profile

Mexazolam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given for its anxiolytic and sedative properties in usual oral doses of 0.5 to 1 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Melex; *Port.*: Sedoxil.

Midazolam *(BAN, rINN)*

Midatsolaami; Midazolám; Midazolamas; Midazolamum; Ro-21-3971; Мидазолам.
8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine.
$C_{18}H_{13}ClFN_3$=325.8
CAS — 59467-70-8.
ATC — N05CD08.
ATC Vet — QN05CD08.
UNII — R60L0SM58C.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Midazolam). A white or yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in methyl alcohol.

USP 36: (Midazolam). A white or yellowish powder. Insoluble in water. Store in airtight containers. Protect from light. The hydrochloride salt of midazolam is soluble in aqueous solutions.

Midazolam Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de midazolam; Midazolam, Chlorhydrate de; Midazolam, hidrocloruro de; Midazolami Hydrochloridum; Ro-21-3981/003; Мидазолама Гидрохлорид.
$C_{18}H_{13}ClFN_3$.HCl=362.2
CAS — 59467-96-8.
ATC — N05CD08.
ATC Vet — QN05CD08.
UNII — W7TTW573JJ.

Incompatibility. The visual compatibility of midazolam hydrochloride with a range of drugs was studied over a period of 4 hours.[1] A white precipitate was formed immediately with dimenhydrinate, pentobarbital sodium, perphenazine, prochlorperazine edisilate, and ranitidine hydrochloride. Similar incompatibility has been reported[2,3] with furosemide, thiopental, and parenteral nutrition solutions. Visual incompatibility of midazolam hydrochloride may be seen if the resultant mixture has a pH of 5 or more;[4,5] however, significant loss of midazolam has also been noted in solutions that remained clear despite an increase in pH.

1. Forman JK, Souney PF. Visual compatibility of midazolam hydrochloride with common preoperative injectable medications. *Am J Hosp Pharm* 1987; 44: 2298–9.
2. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64–5.
3. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1295–300.
4. Swart EL, *et al.* Compatibility of midazolam hydrochloride and lorazepam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; 52: 2020–2.
5. Good PD, *et al.* The compatibility and stability of midazolam and dexamethasone in infusion solutions. *J Pain Symptom Manage* 2004; 27: 471–5.

Stability. Licensed product information states that solutions of midazolam hydrochloride in sodium chloride 0.9%, glucose 5%, or glucose 4% with sodium chloride 0.18% are stable at room temperature for up to 24 hours, and similar solutions containing the equivalent of 500 micrograms/mL of the base were stable for 36 days[1] when stored in glass bottles at temperatures of 4 degrees to 6 degrees, 24 degrees to 26 degrees, and 39 degrees to 41 degrees. Other workers[2] found that a solution containing midazolam hydrochloride equivalent to 1 mg/mL of the base in sodium chloride 0.9% was stable for at least 10 days when stored in PVC bags. The product information advises against admixture with Compound Sodium Lactate Intravenous Infusion (Hartmann's solution) as the potency of midazolam is reduced.

1. Pramar YV, *et al.* Stability of midazolam hydrochloride in syringes and i. v. fluids. *Am J Health-Syst Pharm* 1997; 54: 913–15.
2. McMullin ST, *et al.* Stability of midazolam hydrochloride in polyvinyl chloride bags under fluorescent light. *Am J Health-Syst Pharm* 1995; 52: 2018–20.

Midazolam Maleate *(BANM, USAN, rINNM)*

Maleato de midazolam; Midazolam, Maléate de; Midazolam, maleato de; Midazolami Maleas; Ro-21-3981/001; Мидазолама Малеат.
$C_{18}H_{13}ClFN_3.C_4H_4O_4$=441.8
CAS — 59467-94-6.
ATC — N05CD08.
ATC Vet — QN05CD08.
UNII — 77S20S18SE.

Uses and Administration

Midazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3), except that it has a more potent amnestic action. It is mainly used for sedation (p. 1087.1) in minor surgical or investigative procedures and in intensive care, for premedication, and for induction of general anaesthesia. It is also used as a hypnotic in the short-term (up to 2 weeks) management of insomnia (p. 1086.3) and as an anticonvulsant (for further details, see p. 1086.2). When midazolam is used as a premedicant or for conscious sedation, onset of sedation occurs at about 15 minutes after intramuscular injection reaching a peak at 30 to 60 minutes, and within about 3 to 5 minutes after intravenous injection. When given intravenously as an anaesthetic induction agent, anaesthesia is induced in about 2 to 2.5 minutes; onset of action is more rapid when premedication with an opioid analgesic has been given.

Since the sedative end-point is reached abruptly with midazolam, dosage must be titrated carefully against the response of the patient; lower doses of midazolam are required when it is used with opioid analgesics. Respiratory and cardiac function should be monitored continuously, and facilities for resuscitation should always be available. It is advisable to keep the patient supine during intravenous use and throughout the procedure. Midazolam should be given in reduced doses to **elderly** or **debilitated patients** (see p. 1086.2).

Midazolam is used as the hydrochloride for oral, parenteral, and rectal dosage; the maleate may also be given orally. All doses are given in terms of the base; midazolam hydrochloride 8.3 mg or midazolam maleate 10.2 mg are both equivalent to about 7.5 mg of midazolam.

Total **sedative** doses for dental and minor surgical and other procedures may range from 2.5 to 7.5 mg (about 70 micrograms/kg) *intravenously* although a total dose greater than 5 mg is not usually needed; an initial dose of 2 to 2.5 mg given at a rate of 2 mg/minute 5 to 10 minutes before the start of the procedure has been suggested, with further increments of 0.5 to 1 mg at intervals of at least 2 minutes if required until the desired end-point is reached.

Patients in **intensive care** who require continuous sedation can be given midazolam by *intravenous infusion*. In the UK, an initial intravenous loading dose of 30 to 300 micrograms/kg may be given in increments to induce sedation; each increment of 1 to 2.5 mg should be injected slowly over 20 to 30 seconds, allowing 2 minutes between each dose. In the USA a lower dose of 10 to 50 micrograms/kg (typically about 0.5 to 4 mg) is recommended. The maintenance dose, given by intravenous infusion, varies considerably but a dose of between 20 and 200 micrograms/kg per hour has been suggested. The loading dose should be reduced or omitted, and the maintenance dose reduced, for patients with hypovolaemia, vasoconstriction, or hypothermia. The need for continuous infusion should be reassessed on a daily basis to reduce the risk of accumulation and prolonged recovery. Abrupt withdrawal should be avoided after prolonged use.

Midazolam is given *intramuscularly* as a **premedicant** about 20 to 60 minutes before surgery. The usual dose is about 5 mg; doses range from 70 to 100 micrograms/kg. Alternatively, *intravenous* doses of 1 to 2 mg, repeated if required, may be given 5 to 30 minutes before the procedure.

The usual total dose of midazolam for **induction of anaesthesia** is about 150 to 250 micrograms/kg by slow *intravenous injection* in premedicated patients and 300 to 350 micrograms/kg in those who have not received a premedicant. The desired level of anaesthesia is achieved by stepwise titration; each increment of not more than 5 mg should be injected over 20 to 30 seconds at intervals of 2 minutes. Additional doses may be needed to complete induction; up to 600 micrograms/kg has been used in resistant cases. Further incremental doses of midazolam of about 25% of the induction dose have also been given as a component of the regimens used for the **maintenance of anaesthesia** during short surgical procedures.

Midazolam is also given for sedation in **combined anaesthesia** by *intravenous injection* in a dose of 30 to 100 micrograms/kg repeated as required or by *intravenous infusion* in a dose of 30 to 100 micrograms/kg every hour.

For details of doses in children, see below.

Midazolam maleate is also given *orally* for the short-term management of **insomnia**; the usual dose is the equivalent of midazolam 7.5 to 15 mg at night.

Administration. The rectal,[1] intranasal,[1-5] buccal,[6-11] and sublingual[1,12] routes have all been proposed as alternatives to parenteral use of midazolam.

Intranasal midazolam has caused intense burning, irritation, and lachrymation on instillation, and use of a lidocaine nasal spray has been advocated before giving midazolam to children.[13,14] Alternatively, intranasal delivery of atomised midazolam may cause less discomfort.[15,16] The use of midazolam spray intranasally in adults would be impractical and uncomfortable because of the large volume required. It has therefore been tried as a nebulised solution in adults.[17,18]

1. Wong I, McQueen KD. Midazolam routes of administration. *DICP Ann Pharmacother* 1991; 25: 476–7.
2. Theroux MC, *et al.* Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department. *Pediatrics* 1993; 91: 624–7.
3. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; 77: 529–30.
4. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; 24: 646–51.
5. Ljungman G, *et al.* Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics* 2000; 105: 73–8.
6. Body R, Ijaz M. Buccal midazolam as an alternative to rectal diazepam for prolonged seizures in childhood and adolescence. *Emerg Med J* 2005; 22: 364–5.
7. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; 366: 205–10.
8. Baysun S, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005; 44: 771–6.
9. Baille RK, *et al.* Premedication with buccal midazolam in children and in adults with learning disabilities. *Anaesthesia* 2007; 62: 535–6.
10. Wilson KE, *et al.* Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children: a randomized, cross-over, clinical trial. *Acta Anaesthesiol Scand* 2007; 51: 1062–7.
11. Mpimbaza A, *et al.* Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008; 121: 165–6. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/1/e58 (accessed 23/04/09)
12. Karl HW, *et al.* Transmucosal administration of midazolam for premedication of pediatric patients: comparison of the nasal and sublingual routes. *Anesthesiology* 1993; 78: 885–91.
13. Lugo RA, *et al.* Complication of intranasal midazolam. *Pediatrics* 1993; 92: 638.
14. Chiaretti A, *et al.* Intranasal lidocaine and midazolam for procedural sedation in children. *Arch Dis Child* 2011; 96: 160–3.
15. Gilchrist F, *et al.* The use of intranasal midazolam in the treatment of paediatric dental patients. *Anaesthesia* 2007; 62: 1262–5.
16. Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care* 2008; 24: 300–3.
17. Hodgson PE, *et al.* Administration of nebulized intranasal midazolam to healthy adult volunteers: a pilot study. *Br J Anaesth* 1994; 73: 719P.
18. McCormick ASM, *et al.* Plasma concentrations and sedation scores after nebulized and intranasal midazolam in healthy volunteers. *Br J Anaesth* 2008; 100: 631–6.

INTRATHECAL See Pain, p. 1086.3.

Administration in children. Midazolam may be used in children for **sedation** in minor surgical or investigative procedures. In the UK, the oral and buccal routes are not licensed for this use; however, these routes may be used in children and the following doses, according to age, have been suggested in the *BNFC*:

orally

- 1 month to 18 years: 500 micrograms/kg (maximum of 20 mg) 30 to 60 minutes before the procedure

An oral liquid is available from specialist manufacturers in the UK; alternatively, the injection solution may be diluted with apple or black currant juice, chocolate sauce, or cola.

buccally

- 6 months to 10 years: 200 to 300 micrograms/kg (maximum of 5 mg)

- 10 to 18 years: 6 to 7 mg (maximum of 8 mg if weighing 70 kg or over)

Solutions for buccal use are available from specialist manufacturers in the UK; half the dose should be given between the upper lip and gum on each side of the mouth using an oral syringe and retained for at least 5 minutes before swallowing. [A licensed preparation for buccal use is also available in the UK, however, it is not authorised for use in sedation.]

In the USA, a single oral dose of 250 to 500 micrograms/kg (maximum of 20 mg) is licensed in children aged 6 months and over, although those under 6 years or less cooperative patients may require up to 1 mg/kg.

If the *intravenous* route is more suitable, the following licensed doses may be given according to age:

- 6 months to 5 years: 50 to 100 micrograms/kg up to a total dose of 600 micrograms/kg (but not exceeding 6 mg)
- 6 to 12 years: 25 to 50 micrograms/kg up to a total dose of 400 micrograms/kg (or a maximum of 10 mg)
- older children should be given usual adult doses (see p. 1085.2)

Initial doses should be given over 2 to 3 minutes and an additional interval of 2 to 5 minutes is recommended before giving further doses. Although unlicensed, the *BNFC* suggests that initial doses of midazolam 25 to 50 micrograms/kg may be given intravenously to those aged 1 month and over.

In some countries including the UK, the injection solution may be used *rectally* for sedation in children aged 6 months and over; doses range from 300 to 500 micrograms/kg as a single dose. The injection solution may be diluted with Water for Injections up to a total volume of 10 mL if the volume is too small.

The *intramuscular* route should only be used in children in exceptional cases as such injections are painful; usual doses ranging from 50 to 150 micrograms/kg have been suggested for children aged 1 to 15 years.

Midazolam is also used in children in **intensive care** who require sedation; the following *intravenous* doses are given according to age and adjusted according to response:

- neonates with a gestational age of less than 32 weeks: 60 micrograms/kg per hour by continuous intravenous infusion, reduced after 24 hours to 30 micrograms/kg per hour; treatment duration should not exceed 4 days
- neonates with a gestational age of greater than 32 weeks and infants aged up to 6 months: 60 micrograms/kg per hour by continuous intravenous infusion; treatment duration should not exceed 4 days in neonates
- over 6 months to 12 years: an initial loading dose of 50 to 200 micrograms/kg by intravenous injection over at least 3 minutes; maintenance doses are given as a continuous intravenous infusion and range from 30 to 120 micrograms/kg per hour
- older children should be given usual adult doses (see above)

Loading doses are not recommended in infants aged under 6 months.

A small retrospective observational study[1] of children on prolonged mechanical ventilation (at least 5 days) found that those aged between 1 and 4 years needed higher maintenance doses of midazolam (up to 300 micrograms/kg per hour) when compared with those who were older and younger. The authors also noted that midazolam alone was a poor sedative for all age groups with most children needing additional drugs to maintain adequate sedation.

Midazolam is also used as a **premedicant** and may be given 15 to 30 minutes before the procedure. *Oral* doses are similar to those used for sedation (see above). The *rectal* route is used for premedication in some countries; total doses recommended in the UK in children aged over 6 months range from 300 to 500 micrograms/kg. The *intramuscular* route is also licensed in those aged 1 to 15 years in doses of 80 to 200 micrograms/kg; however, as before, this route should only be used in exceptional circumstances.

For **induction of anaesthesia**, a dose of 150 micrograms/kg by *slow intravenous injection* has been recommended in children over 7 years of age. However, the *BNFC* notes that such use is rare and suggests giving increments of 50 micrograms/kg (maximum of 2.5 mg) over 2 to 5 minutes; after waiting 2 to 5 minutes, additional doses may then be given every 2 minutes, if required, to a maximum total dose of 500 micrograms/kg (not exceeding 25 mg) in those aged up to 18 years.

For the use of midazolam in the management of **status epilepticus**, see Convulsions, below.

Some general references to the use of midazolam in children.[2,3]

1. de Gast-Bakker D-AH, *et al.* Age is of influence on midazolam requirements in a paediatric intensive care unit. *Acta Paediatr* 2007; **96**: 414–17.
2. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998; **35**: 37–47.
3. Marshall J, *et al.* Pediatric pharmacodynamics of midazolam oral syrup. *J Clin Pharmacol* 2000; **40**: 578–89.

Administration in the elderly. Midazolam should be used with caution in patients aged 60 years and over, and those who are debilitated or chronically ill; lower doses should be given and these patients should be continuously monitored for early alterations in vital functions. Peak effects may be reached more slowly in elderly patients than in younger subjects.

For **sedation** in dental and minor surgical and other procedures, an initial dose of 0.5 to 1.5 mg given *intravenously* at a maximum rate of 2 mg/minute 5 to 10 minutes beforehand has been suggested, with further increments of 0.5 to 1 mg if required to a usual maximum total dose of 3.5 mg or until the desired end-point is reached.

For continuous sedation in **intensive care**, the usual adult dose (see p. 1085.2) may be given.

Midazolam is given *intramuscularly* as a **premedicant** about 20 to 60 minutes before surgery. The usual dose is 2 to 3 mg (doses range from 20 to 50 micrograms/kg). Alternatively, an initial *intravenous* dose of 500 micrograms, repeated slowly if required, may be given 5 to 30 minutes before the procedure.

The usual total dose for **induction of anaesthesia** is 50 to 150 micrograms/kg by slow *intravenous injection* in premedicated patients and 150 to 300 micrograms/kg in those who have not received a premedicant. Lower doses (up to 250 micrograms/kg) may be sufficient in severely ill or debilitated patients who have not received a premedicant. The desired level of anaesthesia is achieved by *stepwise titration*. Further incremental doses of midazolam of about 25% of the induction dose have also been given as a component of the regimens used for the **maintenance of anaesthesia** during short surgical procedures.

For sedation in **combined anaesthesia**, lower maintenance doses will be required (see above for the usual adult dose).

Midazolam maleate is also given *orally* for the short-term management of **insomnia**; the usual dose is the equivalent of midazolam 7.5 mg at night.

Conversion and dissociative disorders. For reference to the use of midazolam in the diagnosis of conversion disorders, such as hysterical paralysis, see p. 1064.2.

Convulsions. Benzodiazepines such as diazepam or lorazepam given parenterally are often tried first to control status epilepticus (p. 510.2). Midazolam has been used as an alternative.[1] It may be of value when intravenous access is difficult as effective concentrations of midazolam can be obtained after intramuscular injection.[2,3] The *BNF* considers it to be the benzodiazepine of choice when a continuous subcutaneous infusion is required for the control of convulsions, such as in palliative care, and states that it may be given in an initial dose of 20 to 40 mg every 24 hours. Intravenous midazolam has been used in some centres[4] for status epilepticus refractory to diazepam, lorazepam, or phenytoin but reviews of the literature[5] reveal that evidence of efficacy is limited mainly to uncontrolled studies and anecdotal reports. The *BNFC* states that for the treatment of status epilepticus or febrile convulsions, a dose of midazolam of 1 microgram/kg per minute by continuous intravenous infusion may be given to neonates, children, and adolescents up to 18 years of age after an initial loading dose of 150 to 200 micrograms/kg. The infusion rate may be increased by 1 microgram/kg per minute every 15 minutes until the seizure is controlled or until a maximum of 5 micrograms/kg per minute is reached. Higher intravenous doses of midazolam have been advocated by some[6] for children with refractory status epilepticus.

The intranasal[7,8] and buccal[9] routes have also been used for the management of seizures, and UK guidelines[10] consider buccal midazolam an alternative to rectal diazepam for initial management of status epilepticus in the home setting or where intravenous access is not possible. In addition, studies[11–13] found that buccal midazolam was more effective than rectal diazepam for treatment of children with seizures in the hospital setting and did not appear to increase the risk of respiratory depression. Results from another study[14] also suggested that buccal midazolam can be used as an alternative to intravenous diazepam, particularly where intravenous access is difficult to establish. The *BNF* states that a dose of midazolam 10 mg, repeated once after 10 minutes if necessary, may be given by the buccal route to adults aged 18 years and over. The *BNFC* suggests giving the following buccal doses, which may be repeated once after 10 minutes if necessary, according to age:

- neonate to 3 months: 300 micrograms/kg (maximum of 2.5 mg)
- 3 months to 1 year: 2.5 mg
- 1 to 5 years: 5 mg
- 5 to 10 years: 7.5 mg
- 10 to 18 years: 10 mg

A proprietary buccal solution is licensed in the EU for use in children aged from 3 months to under 18 years and is given in similar doses; product information advises that those aged between 3 and 6 months should be treated in a hospital setting.

Midazolam has also been tried[15] in the management of acute convulsions associated with severe malaria in children.

1. Hanley DF, *et al.* Use of midazolam in the treatment of refractory status epilepticus. *Clin Ther* 1998; **20**: 1093–1105.
2. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1**: 26–44.
3. Towne AR, DeLorenzo RJ. Use of intramuscular midazolam for status epilepticus. *J Emerg Med* 1999; **17**: 323–8.
4. Bebin M, Bleck TP. New anticonvulsant drugs: focus on flunarizine, fosphenytoin, midazolam and stiripentol. *Drugs* 1994; **48**: 153–71.
5. Denzel D, Burstein AH. Midazolam in refractory status epilepticus. *Ann Pharmacother* 1996; **30**: 1481–3.
6. Morrison G, *et al.* High-dose midazolam therapy for refractory status epilepticus in children. *Intensive Care Med* 2006; **32**: 2070–6.
7. Wallace SJ. Nasal benzodiazepines for management of acute childhood seizures? *Lancet* 1997; **349**: 222.
8. Lahat E, *et al.* Intranasal midazolam for childhood seizures. *Lancet* 1998; **352**: 620.
9. Scott RC, *et al.* Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999; **353**: 623–6.
10. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020NICEguideline.pdf (accessed 21/08/08)
11. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366**: 205–10.
12. Baysun S, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005; **44**: 771–6.
13. Mpimbaza A, *et al.* Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008; **121**: 165–6. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/1/e58 (accessed 23/04/09)
14. Talukdar B, Chakrabarty B. Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. *Brain Dev* 2009; **31**: 744–9.
15. Muchohi SN, *et al.* Pharmacokinetics and clinical efficacy of midazolam in children with severe malaria and convulsions. *Br J Clin Pharmacol* 2008; **66**: 529–38.

Disturbed behaviour. For a discussion of the palliative treatment of terminal restlessness with benzodiazepines such as midazolam, see p. 1030.2.

Dyspnoea. Benzodiazepines such as midazolam may relieve dyspnoea in patients with advanced cancer, especially when this is associated with anxiety (see also Diazepam, p. 1064.2). Subcutaneous doses of midazolam of 5 mg every 4 hours have been combined successfully with morphine.[1] Midazolam has also been suggested[2] as an alternative to chlorpromazine in patients with advanced cancer and intractable dyspnoea to relieve air hunger and to sedate dying patients who have unrelieved distress.

1. Navigante AH, *et al.* Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage* 2006; **31**: 38–47.
2. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342**: 450–1.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Midazolam given intravenously or subcutaneously has been reported[1,2] to have been effective in 3 patients with metastatic cancer who had hiccups unresponsive to conventional treatment. However, it has been noted[1,3] that benzodiazepines such as midazolam may exacerbate or precipitate hiccups.

1. Wilcock A, Twycross R. Midazolam for intractable hiccup. *J Pain Symptom Manage* 1996; **12**: 59–61.
2. Moro C, *et al.* Midazolam for long-term treatment of intractable hiccup. *J Pain Symptom Manage* 2005; **29**: 221–3.
3. Rousseau P. Hiccups. *South Med J* 1995; **88**: 175–81.

Insomnia. For discussion of the management of insomnia including limitations on the use of benzodiazepines and a recommendation that the period of treatment with midazolam should be limited to 2 weeks, see p. 1033.2.

References.

1. Monti JM, *et al.* The effect of midazolam on transient insomnia. *Eur J Clin Pharmacol* 1993; **44**: 525–7.

Nausea and vomiting. Midazolam has been tried[1–5] for the prophylaxis of postoperative nausea and vomiting.

1. Rodolà F. Midazolam as an anti-emetic. *Eur Rev Med Pharmacol Sci* 2006; **10**: 121–6.
2. Lee Y, *et al.* Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomised controlled trial. *Anaesthesia* 2007; **62**: 18–22.
3. Riad W, *et al.* Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children. *Eur J Anaesthesiol* 2007; **24**: 697–701.
4. Jung JS, *et al.* Prophylactic antiemetic effect of midazolam after middle ear surgery. *Otolaryngol Head Neck Surg* 2007; **137**: 753–6.
5. Tarhan Ö, *et al.* Subhypnotic doses of midazolam prevent nausea and vomiting during spinal anesthesia for cesarean section. *Minerva Anestesiol* 2007; **73**: 629–33.

Pain. The conventional use of benzodiazepines in pain management is as muscle relaxants to relieve pain associated with skeletal muscle spasm (see under Choice of Analgesic, p. 4.2). Midazolam has been studied[1–7] for use

as an intrathecal analgesic but, because of some uncertainty about its risk and benefits, its use has been uncommon. A meta-analysis[8] of 13 studies found that the use of intrathecal midazolam as an adjunct to spinal anaesthesia improved perioperative or peripartum analgesia and reduced the incidence of postoperative nausea and vomiting, particularly when used for caesarean section; the authors considered that further study of its safety was warranted although neurological symptoms were rare and not significantly increased when compared with placebo.

1. Cripps TP, Goodchild CS. Intrathecal midazolam and the stress response to upper abdominal surgery. *Clin J Pain* 1988; 4: 125–8.
2. Serrao JM, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. *Pain* 1992; 48: 5–12.
3. Baaljens FFJ, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a randomized double-blind placebo-controlled study. *Br J Anaesth* 1995; 74 (suppl 1): 143.
4. Valentine JMJ, *et al.* The effect of intrathecal midazolam on post-operative pain. *Eur J Anaesthesiol* 1996; 13: 589–93.
5. Batra YK, *et al.* Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. *Int J Clin Pharmacol Ther* 1999; 37: 519–23.
6. Duncan MA, *et al.* Prospective audit comparing intrathecal analgesia (incorporating midazolam) with epidural and intravenous analgesia after major open abdominal surgery. *Anaesth Intensive Care* 2007; 35: 558–62.
7. Murali Krishna T, *et al.* Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. *Eur J Anaesthesiol* 2008; 25: 299–306.
8. Ho KM, Ismail H. Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. *Anaesth Intensive Care* 2008; 36: 365–73.

Premedication and sedation. Midazolam is used as a premedicant (see Anaesthesia, p. 1899.1) and as a sedative (p. 1032.2) for therapeutic and investigative procedures such as dental treatment (p. 1032.2) and endoscopy (see below). It is also used to provide continuous sedation in patients in intensive care (p. 1033.1) although a systematic review has raised concerns about such use in neonates (see also Children under Precautions, below).

References.

1. Sandler ES, *et al.* Midazolam versus fentanyl as premedication for painful procedures in children with cancer. *Pediatrics* 1992; 89: 631–4.
2. Jacqz-Aigrain E, *et al.* Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet* 1994; 344: 646–50.
3. McErlean M, *et al.* Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion. *J Pediatr* 2003; 142: 429–30.
4. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003; 327: 708–11.
5. Ng E, *et al.* Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/03/06).
6. Averley PA, *et al.* An RCT pilot study to test the effects of intravenous midazolam as a conscious sedation technique for anxious children requiring dental treatment: an alternative to general anaesthesia. *Br Dent J* 2004; 197: 553–8.
7. Lam C, *et al.* Midazolam premedication in children: a pilot study comparing intramuscular and intranasal administration. *Anesth Prog* 2005; 52: 56–61.
8. Wilson KE, *et al.* A comparison of oral midazolam and nitrous oxide sedation for dental extractions in children. *Anaesthesia* 2006; 61: 1138–44.

ENDOSCOPY. Intravenous benzodiazepines such as diazepam or midazolam are often the preferred drugs for sedation in patients undergoing endoscopy (p. 1032.3). They are sometimes used with opioid analgesics for sedation.[1]

A reduced dose of midazolam was required for endoscopy when it was given as a bolus intravenous injection rather than as a slow intravenous titration. A study in 788 patients undergoing endoscopy found that a mean dose of 4.65 mg of midazolam given as a bolus intravenous injection was safe and effective in patients under 70 years of age whereas a mean dose of 1.89 mg was sufficient for patients over 70 years of age.[2] Furthermore, topical pharyngeal anaesthesia was not required with these doses of midazolam. Intravenous boluses were also easier to give and associated with less oxygen desaturation than titrating the dose.[3] Another study found that even lower doses of midazolam (35 micrograms/kg) were effective as premedication before gastroscopy, and were associated with fewer complications than higher doses (70 micrograms/kg).[4]

Intranasal[5] and oral[6,7] midazolam have also been tried for sedation before endoscopy, particularly in children.[5,6]

1. Mamula P, *et al.* Safety of intravenous midazolam and fentanyl for pediatric GI endoscopy: prospective study of 1578 endoscopies. *Gastrointest Endosc* 2007; 65: 203–10.
2. Smith MR, *et al.* Small bolus injections of intravenous midazolam for upper gastrointestinal endoscopy: a study of 788 consecutive cases. *Br J Clin Pharmacol* 1993; 36: 573–8.
3. Morrow JB, *et al.* Sedation for colonoscopy using a single bolus is safe, effective, and efficient: a prospective, randomized, double-blind trial. *Am J Gastroenterol* 2000; 95: 2242–7.
4. Campo R, *et al.* Efficacy of low and standard midazolam doses for gastroscopy: a randomized, double-blind study. *Eur J Gastroenterol Hepatol* 2000; 12: 187–90.
5. Fishbein M, *et al.* Evaluation of intranasal midazolam in children undergoing esophagogastroduodenoscopy. *J Pediatr Gastroenterol Nutr* 1997; 25: 261–6.
6. Martinez JL, *et al.* A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy. *J Pediatr Gastroenterol Nutr* 2002; 35: 51–8.
7. Mui LM, *et al.* Premedication with orally administered midazolam in adults undergoing diagnostic upper endoscopy: a double-blind placebo-controlled randomized trial. *Gastrointest Endosc* 2005; 61: 195–200.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Withdrawal symptoms have been reported[1,2] in children after stopping midazolam, which had been used for sedation during mechanical ventilation; in the majority of cases, midazolam had been given with an opioid which can confound symptoms of benzodiazepine withdrawal.[2]

1. van Engelen BGM, *et al.* Benzodiazepine withdrawal reaction in two children following discontinuation of sedation with midazolam. *Ann Pharmacother* 1993; 27: 579–81.
2. Ista E, *et al.* Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. *Crit Care Med* 2008; 36: 2427–32.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. There have been reports of life-threatening adverse respiratory and cardiovascular events occurring after use of midazolam; when giving midazolam the precautions given under Incidence of Adverse Effects, below should be observed to lessen the risk of such reactions. Pain, tenderness, and thrombophlebitis have occurred after injection of midazolam. Hiccups have been reported.

Incidence of adverse effects. Death due to respiratory depression, hypotension, or cardiac arrest has been reported in patients given intravenous midazolam for conscious sedation.[1] Within about 6 months of its introduction in the USA in May 1986, 13 fatalities due to cardiorespiratory depression had been reported (higher doses were used initially in the USA than those in the UK). By January 1988, 66 deaths had been reported, although in November 1987 the adult dosage recommendation had been reduced to 70 micrograms/kg and to 50 micrograms/kg for elderly patients. Fatalities have also occurred in the UK [where the dose is 70 micrograms/kg, reduced in the elderly] with 4 deaths reported to the UK CSM by November 1987.

While it appears that midazolam and diazepam produce very similar degrees of hypoventilation and oxygen desaturation when used in equivalent doses,[2] the sedative end-point does appear to be reached more abruptly with midazolam.[3] Licensed product information recommends that the following precautions should therefore be taken:

- facilities for resuscitation should always be available when intravenous midazolam is used
- respiratory and cardiac function should be monitored continuously
- the dose of midazolam should be carefully titrated against the response of the patient and the product recommendations concerning dosage rate be observed
- particular care, including a reduction in midazolam dosage, is required in patients also receiving opioid analgesics, in the elderly and children, and in debilitated or chronically ill patients such as those with compromised cardiorespiratory function, chronic renal failure, or hepatic impairment
- similar warnings apply to the use of oral midazolam where it is available

The National Patient Safety Agency[4] in the UK has also issued guidelines on the use of midazolam for conscious sedation after it had received 498 reports (3 fatalities) of inappropriate dosage, particularly with high-strength preparations, for such use between November 2004 and November 2008.

The availability of the benzodiazepine antagonist, flumazenil, should not be an encouragement to use larger doses of midazolam.[1]

Since endoscopy of the upper gastrointestinal tract can itself reduce oxygen saturation, some workers have advocated the prophylactic use of nasal oxygen during this procedure for those patients at particular risk as outlined above.

1. Anonymous. Midazolam—is antagonism justified? *Lancet* 1988; ii: 140–2.
2. Bell GD. Review article: premedication and intravenous sedation for upper gastrointestinal endoscopy. *Aliment Pharmacol Ther* 1990; 4: 103–22.
3. Ryder W, Wright PA. Dental sedation: a review. *Br Dent J* 1988; 165: 207–16.
4. National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR011: reducing risk of overdose with midazolam injection in adults (issued 9th December, 2008). Available at: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59896 (accessed 11/11/10)

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of midazolam on breast-fed infants was unknown its use by mothers during breast feeding might be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Midazolam could not be detected in breast milk from 11 mothers the morning after either the first or the fifth nightly 15-mg oral dose.[2] Additional study of 2 mothers found that midazolam and its hydroxy-metabolite disappeared rapidly from milk with undetectable concentrations at 4 hours. The mean milk to plasma ratio for midazolam was 0.15 in 6 paired samples. Another study[3] using midazolam 2 mg intravenously for pre-operative sedation in 5 mothers concluded that the amount of midazolam excreted into breast milk within 24 hours after administration was less than 0.1% of the maternal dose, and hence unlikely to affect a healthy full-term breast-feeding infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; 30: 787–93.
3. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; 79: 549–57.

Children. An intravenous bolus injection of midazolam in children already receiving intravenous morphine after cardiac surgery produced an undesirable transient fall in cardiac output.[1] It was suggested that for patients already receiving other drugs that provide sedation the use of midazolam in the early postoperative period should be limited to a continuous infusion. Similarly, it has been recommended[2] that bolus intravenous doses of midazolam should be avoided in neonates due to the occurrence of hypotension.

The initial dosage of midazolam used for continuous intravenous sedation may need to be reduced in critically ill children under 3 years of age since the plasma clearance of midazolam appears to be reduced in these patients.[3]

1. Shekerdemian L, *et al.* Cardiovascular effects of intravenous midazolam after open heart surgery. *Arch Dis Child* 1997; 76: 57–61.
2. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; 31: 423–43.
3. Hughes J, *et al.* Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996; 30: 27–30.

Effects on mental function. For discussion of the adverse effects of benzodiazepines on mental function, including reports of sexual fantasies in women sedated with intravenous midazolam, see Diazepam, p. 1066.1.

Effects on the nervous system. For reference to acute dystonia associated with use of midazolam, see Diazepam, p. 1066.1.

ENCEPHALOPATHY. For a report of prolonged use of midazolam with fentanyl being associated with encephalopathy in infants sedated under intensive care, see Diazepam, p. 1066.2.

MYOCLONUS. Myoclonic twitching of all four limbs was noted[1] in 6 of 102 neonates who received a continuous intravenous infusion of midazolam at a rate of 30 to 60 micrograms/kg per hour. Myoclonus ceased a few hours after stopping the infusion and never recurred. No ictal activity was detected in EEGs recorded during the myoclonus.

1. Magny JF, *et al.* Midazolam and myoclonus in neonate. *Eur J Pediatr* 1994; 153: 389–90.

The elderly. Sedation with midazolam in elderly subjects needed only about half the dose necessary to produce comparable effects in younger subjects.[1] Pharmacodynamic differences due to age suggested an increase in sensitivity of the CNS to midazolam in the elderly subjects.

1. Albrecht S, *et al.* The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther* 1999; 65: 630–9.

Hepatic impairment. For the precautions to be observed in patients with impaired liver function, see under Pharmacokinetics, p. 1088.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies midazolam as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Renal impairment. Five patients with severe renal impairment had prolonged sedation when given midazolam; this was attributed to accumulation of conjugated metabolites.[1]

1. Bauer TM, *et al.* Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; 346: 145–7.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Absorption of midazolam is rapid, peak plasma concentrations occurring within 20 to 60 minutes of a dose, depending on the route. Extensive first-pass metabolism results in a low systemic bioavailability after oral doses. Bioavailability is higher, but variable, after intramuscular injection; figures of more than 90% are often cited.

Midazolam is lipophilic at physiological pH. It crosses the placenta and is distributed into breast milk (but see p. 1087.2). Midazolam is about 96 to 98% bound to plasma proteins, mainly albumin.

Midazolam usually has a short elimination half-life of about 1.5 to 2.5 hours although half-lives up to 6 times longer have been reported in critically ill patients. The half-life of midazolam is also prolonged in neonates, in the elderly, and in patients with liver disorders or cardiac insufficiency.

Midazolam is metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4. The major metabolite, 1-hydroxymidazolam (alpha-hydroxymidazolam) has some activity; its half-life is less than 1 hour. Midazolam metabolites are excreted in the urine, mainly as glucuronide conjugates.

References.
1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; 16: 337–64.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; 57: 135–45.

Children. In a study[1] of the pharmacokinetics of midazolam in children the bioavailability of a dose of 150 micrograms/kg was 100, 87, 27, and 18% when given by the intravenous, intramuscular, oral, and rectal routes, respectively. The oral bioavailability was reduced to 16 and 15% after increasing the dose to 450 micrograms/kg and 1 mg/kg, respectively. There was bioequivalence between the 150 micrograms/kg intramuscular dose and the 450 micrograms/kg oral dose from 45 to 120 minutes after dosage. Absorption from the rectal route gave lower serum-midazolam concentrations than the oral route at the 150 micrograms/kg dose.

Midazolam appears to be absorbed rapidly when given intranasally to children with mean peak plasma concentrations being achieved within about 12 minutes;[2-4] values of 30 and 55% have been reported for the bioavailability[3,4] but methods to optimise nasal delivery have resulted in higher bioavailability in studies in adults (see below). A study comparing intranasal, intravenous, and rectal dosage of midazolam in children found that plasma concentrations from 45 minutes after intranasal and intravenous doses were similar; those after rectal doses were consistently less than after these other 2 routes.[2] Possible reasons suggested by the authors for this included the effect that the wide interindividual variations in rectal pH may have had on the absorption of midazolam.

Another study has investigated the relationship between intravenous dose and plasma-midazolam concentrations in children.[5]

See also under Precautions, p. 1087.3.

1. Payne K, *et al.* The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989; 37: 267–72.
2. Malinovsky J-M, *et al.* Plasma concentrations of midazolam after iv, nasal or rectal administration in children. *Br J Anaesth* 1993; 70: 617–20.
3. Rey E, *et al.* Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol* 1991; 41: 355–7.
4. Kauffman RE, *et al.* Intranasal absorption of midazolam. *Clin Pharmacol Ther* 1995; 57: 209.
5. Tolia V, *et al.* Pharmacokinetic and pharmacodynamic study of midazolam in children during esophagogastroduodenoscopy. *J Pediatr* 1991; 119: 467–71.

NEONATES. References[1-7] to the pharmacokinetics of midazolam in neonates.

1. Jacqz-Aigrain E, *et al.* Pharmacokinetics of midazolam in critically ill neonates. *Eur J Clin Pharmacol* 1990; 39: 191–2.
2. Jacqz-Aigrain E, *et al.* Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *Eur J Clin Pharmacol* 1992; 42: 329–32.
3. Burtin P, *et al.* Population pharmacokinetics of midazolam in neonates. *Clin Pharmacol Ther* 1994; 56: 615–25.
4. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; 31: 423–43.
5. Harte GJ, *et al.* Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997;33: 335–8.
6. Lee TC, *et al.* Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. *Anesthesiology* 1999; 90: 451–7.
7. de Wildt SN, *et al.* Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther* 2001; 70: 525–31.

Half-life. Data collected from 7 studies involving 90 subjects have suggested that the prolonged midazolam half-lives reported in a small number of patients are secondary to increases in the volume of distribution and not a result of alterations in clearance and metabolism.[1] Prolongation of the half-life of midazolam has been reported[2] in 2 patients after sustained infusion for status epilepticus.

1. Wills RJ, *et al.* Increased volume of distribution prolongs midazolam half-life. *Br J Clin Pharmacol* 1990; 29: 269–72.
2. Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology* 2000 54: 1366–8.

Intranasal administration. Plasma concentrations of midazolam sufficient to induce conscious sedation are rapidly attained after intranasal doses.[1] Although bioavailability of up to 55% had previously been obtained in children after intranasal use (see above), slow administration and other methods to optimise nasal delivery have resulted in higher bioavailability in adults; a mean ranging from 72.5 to 92% has been reported in some studies.[2-5]

1. Burstein AH, *et al.* Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. *J Clin Pharmacol* 1997; 37: 711–18.
2. Björkman S, *et al.* Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. *Br J Anaesth* 1997; 79: 575–80.
3. Knoester PD, *et al.* Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray: a study in healthy volunteers. *Br J Clin Pharmacol* 2002; 53: 501–7.
4. Wermeling DP, *et al.* Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. *Anesth Analg* 2006; 103: 344–9.
5. Haschke M, *et al.* Pharmacokinetics and pharmacodynamics of nasally delivered midazolam. *Br J Clin Pharmacol* 2010; 69: 607–16.

Liver disorders. The pharmacokinetics of midazolam in patients with advanced cirrhosis of the liver were characterised by an increase in oral systemic bioavailability[1] and by a decrease in clearance with consequent prolongation of elimination half-life.[1,2] Dosage may need to be reduced. However, metabolism of midazolam has been found in the anhepatic period of liver transplantation indicating extrahepatic metabolism (see below).

1. Pentikäinen PJ, *et al.* Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989; 29: 272–7.
2. MacGilchrist AJ, *et al.* Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. *Gut* 1986; 27: 190–5.

Metabolism. For a discussion of the metabolism of benzodiazepines, see Diazepam, p. 1071.1. Midazolam appears to be metabolised by at least 3 different cytochrome P450 isoenzymes found in the liver and in the kidney.[1] Variations in the activity of these enzymes might account for some of the interindividual differences in pharmacokinetics and pharmacodynamics seen with midazolam.[2] However, a study[3] in patients undergoing liver transplantation has indicated that the small intestine is a significant site for the first-pass metabolism of midazolam, metabolism presumably being catalysed by the cytochrome P450 isoenzyme CYP3A4 found in intestinal mucosa.

1. Wandel C, *et al.* Midazolam is metabolized by at least three different cytochrome P450 enzymes. *Br J Anaesth* 1994; 73: 658–61.
2. Lown KS, *et al.* The erythromycin breath test predicts the clearance of midazolam. *Clin Pharmacol Ther* 1995; 57: 16–24.
3. Paine MF, *et al.* First-pass metabolism of midazolam by the human intestine. *Clin Pharmacol Ther* 1996; 60: 14–24.

Sublingual administration. High bioavailability (about 75%) and reliable plasma concentrations have been achieved after sublingual doses of midazolam.[1]

1. Schwagmeier R, *et al.* Midazolam pharmacokinetics following intravenous and buccal administration. *Br J Clin Pharmacol* 1998; 46: 203–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dalam; Dormicum; Dormid; Drimnorth; Gobbizolam; Rem; Ukel†; ***Austral.***: Hypnovel; ***Austria***: Dormicum; ***Belg.***: Dormicum; ***Braz.***: Dormant; Dormire; Dormium; Dormonid; Hipnazolam; Midadorm; ***Chile***: Dormonid; Noctura; Terap; Zolmid; ***China***: Dormicum (多美康); Fulsed (弗赛得); Li Yue Xi (力月西); ***Cz.***: Dormicum; Fulsed†; ***Denm.***: Dormicum†; ***Fin.***: Dormicum; ***Fr.***: Hypnovel; Versed; ***Ger.***: Buccolam; Dormicum; ***Gr.***: Damizol; Dormicum; Dormixal; Epistatus; ***Hong Kong***: Dormicum; ***Hung.***: Dormicum; ***India***: Benzosed; Fulsed; Mezolam; Miben; Midapic; Midaz; Midosed; Midzee; Midzol; ***Indon.***: Anesfar; Dormicum; Fortanest; Hipnoz; Miloz; Sedacum; Sezolam; ***Irl.***: Buccolam; Hypnovel; ***Israel***: Midazol†; Midolam; ***Ital.***: Ipnovel; ***Malaysia***: Domi; Dormicum; Fulsed; Mizolam; ***Mex.***: Dormicum; Midozor; Relacum; Zomsol†; ***Neth.***: Dormicum; ***Norw.***: Dormicum†; ***NZ***: Hypnovel; ***Philipp.***: Dormicum; Dormizol; Sedoz; ***Pol.***: Dormicum; Midanium; Sopodorm; ***Port.***: Dormicum; Zolamid; ***Rus.***: Dormicum (Дормикум); Fulsed (Фулсед); ***S.Afr.***: Dormicum; Midacum; Midanium†; Midazoject; ***Singapore***: Domi; Dormicum; Fulsed; ***Spain***: Dormicum; ***Swed.***: Dormicum; ***Switz.***: Dormicum; ***Thai.***: Dormicum†; ***Turk.***: Demizolam; Dormicum; ***UK***: Buccolam; Hypnovel; ***Ukr.***: Fulsed (Фулсед); ***Venez.***: Benzosed; Doricum; Midazepin.

Pharmacopoeial Preparations
BP 2014: Midazolam Injection; Midazolam Oral Solution; Midazolam Oromucosal Solution;
USP 36: Midazolam Injection.

Molindone Hydrochloride *(BANM, USAN, rINNM)*

EN-1733A; Hidrocloruro de molindona; Molindona, hidrocloruro de; Molindone, Chlorhydrate de; Molindoni Hydrochloridum; Молиндона Гидрохлорид.

3-Ethyl-1,5,6,7-tetrahydro-2-methyl-5-(morpholinomethyl) indol-4-one hydrochloride.

$C_{16}H_{24}N_2O_2$,HCl=312.8

CAS — 7416-34-4 (molindone); 15622-65-8 (molindone hydrochloride).

ATC — N05AE02.

ATC Vet — QN05AE02.

UNII — 1DWS68PNE6.

Pharmacopoeias. In *US.*

USP 36: (Molindone Hydrochloride). pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Profile

Molindone is an indole derivative with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.2). It has been given orally as the hydrochloride for the treatment of psychoses including schizophrenia.

Psychiatric disorders. A systematic review[1] found that, based on limited data, molindone appeared to be effective in schizophrenia (p. 1031.3) and other severe psychoses but evidence of differences from other classical antipsychotics was lacking. However, weight loss appears to be more prominent (see p. 1047.3).

1. Bagnall A-M, *et al.* Molindone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 04/09/13).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Moban†.

Pharmacopoeial Preparations
USP 36: Molindone Hydrochloride Tablets.

Moperone Hydrochloride *(rINNM)*

Hidrocloruro de moperona; Methylperidol Hydrochloride; Moperona, hidrocloruro de; Mopérone, Chlorhydrate de; Moperoni Hydrochloridum; R-1658 (moperone); Монерона Гидрохлорид.

4'-Fluoro-4-(4-hydroxy-4-*p*-tolylpiperidino)butyrophenone hydrochloride.

$C_{22}H_{26}FNO_2$,HCl=391.9

CAS — 1050-79-9 (moperone); 3871-82-7 (moperone hydrochloride).

ATC — N05AD04.

ATC Vet — QN05AD04.

Profile

Moperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It has been given orally for the treatment of psychoses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Luvatren†.

Mosapramine *(rINN)*

Clospipramine; Mosapramina; Mosapraminum; Y-516; Мозапрамин.

(±)-1'-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-5-yl) propyl]hexahydrospiro[imidazo[1,2-*a*]pyridine-3(2*H*),4'-piperidin]-2-one.

$C_{28}H_{33}ClN_4O$=479.1

CAS — 89419-40-9 (mosapramine); 98043-60-8 (mosapramine hydrochloride).

ATC — N05AX10.

ATC Vet — QN05AX10.

UNII — 04UZQ7O95J.

Profile

Mosapramine is an antipsychotic that is used as the hydrochloride in the treatment of schizophrenia.

References.
1. Ishigooka J, *et al.* Pilot study of plasma concentrations of mosapramine, a new iminodibenzyl antipsychotic agent, after multiple oral administration in schizophrenic patients. *Curr Ther Res* 1994; 55: 331–42.
2. Takahashi N, *et al.* Comparison of risperidone and mosapramine addition to neuroleptic treatment in chronic schizophrenia. *Neuropsychobiology* 1999; 39: 81–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cremin.

Nemonapride *(rINN)*

Emonapride; Nemonaprida; Némonapride; Nemonapridum; YM-09151-2; Немонаприд.

(±)-*cis*-*N*-(1-Benzyl-2-methyl-3-pyrrolidinyl)-5-chloro-4-(methylamino)-o-anisamide.

$C_{21}H_{26}ClN_3O_2$=387.9

CAS — 93664-94-9.

UNII — Q88T5P3444.

Profile

Nemonapride is a substituted benzamide antipsychotic with general properties similar to those of sulpiride (p. 1107.3). It is given orally in the treatment of schizophrenia (p. 1031.3) in usual doses of 9 to 36 mg daily in divided doses; up to 60 mg daily may be given if necessary.

References.

1. Satoh K, *et al.* Effects of nemonapride on positive and negative symptoms of schizophrenia. *Int Clin Psychopharmacol* 1996; 11: 279–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Emilace (艾敏斯); *Jpn*: Emilace.

Nimetazepam *(rINN)*

Menifazepam; Nimétazépam; Nimetazepamum; S-1530; Ниметазепам.

1,3-Dihydro-1-methyl-7-nitro-5-phenyl-1,4-benzodiazepin-2-one.

$C_{16}H_{13}N_3O_3$=295.3

CAS — 2011-67-8.

UNII — 4532264KW6.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nimetazepam:

Happy 5

Profile

Nimetazepam is a benzodiazepine with the general properties of diazepam (p. 1063.2). It has been given for the short-term management of insomnia (p. 1033.2) in a usual oral dose of 3 or 5 mg at night. It appears to have been subject to abuse, especially in South East Asia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Erimin.

Nitrazepam *(BAN, USAN, rINN)*

Nitratsepaami; Nitrazepám; Nitrazépam; Nitrazepamas; Nitrazepamum; NSC-58775; Ro-5-3059; Ro-4-5360; Нитразепам.

1,3-Dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{11}N_3O_3$=281.3

CAS — 146-22-5.

ATC — N05CD02.

ATC Vet — QN05CD02.

UNII — 9CLV70W7HS.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nitrazepam:

Don; Moggies; Moogles; Nitro's; The Don.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn*.

Ph. Eur. 8: (Nitrazepam). A white or yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

Uses and Administration

Nitrazepam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (p. 1033.2) and is reported to act in 30 to 60 minutes to produce sleep lasting for 6 to 8 hours. Nitrazepam has also been used in epilepsy, notably for infantile spasms (below).

The usual oral dose for insomnia is 5 mg at night, although 10 mg may be required in some patients. Elderly or debilitated patients should not be given more than half of the usual adult dose.

Administration in children. For details of doses of nitrazepam in children, see Epilepsy, below.

Epilepsy. Benzodiazepines are sometimes employed in the management of epilepsy (p. 506.1), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Nitrazepam has perhaps been most useful in the treatment of infantile spasms (as for example in West's syndrome) and the so-called infantile myoclonic seizures. The *BNFC* suggests that those aged from 1 month to 2 years may be given initial oral doses of 125 micrograms/kg twice daily, adjusted according to response over 2 to 3 weeks to 250 micrograms/kg twice daily (maximum of 500 micrograms/kg, but not exceeding 5 mg, twice daily); the same total daily dose may also be given in 3 divided doses. There has been concern, however, over swallowing difficulties with subsequent aspiration and reports of unexpected death associated with the use of nitrazepam in young children (see Effects on the Digestive System under Adverse Effects, below).

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 5 mg of nitrazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Effects on the digestive system. Two children given nitrazepam as part of their antiepileptic therapy developed drooling, eating difficulty, and aspiration pneumonia; symptoms improved in one patient when the dosage of nitrazepam was reduced.[1] Manometric studies indicated that the onset of normal cricopharyngeal relaxation in swallowing was delayed in these patients until after hypopharyngeal contraction, resulting in impaired swallowing and spillover of material into the trachea. Other workers[2] have found similar effects on swallowing and cricopharyngeal relaxation in children given nitrazepam. The deaths of 6 epileptic children under 5 years of age who were treated with nitrazepam have been reported.[3] Three of the deaths were unexpected, and in view of the previous reports of swallowing difficulties and aspiration, it was recommended that the use of nitrazepam in young children be restricted to those in whom seizure control fails to improve with other antiepileptics. Another study[4] also found an apparently increased risk of death, especially in young patients with intractable epilepsy, associated with nitrazepam therapy.

1. Wyllie E, *et al.* The mechanism of nitrazepam-induced drooling and aspiration. *N Engl J Med* 1986; 314: 35–8.
2. Lim HCN, *et al.* Nitrazepam-induced cricopharyngeal dysphagia, abnormal esophageal peristalsis and associated bronchospasm: probable cause of nitrazepam-related sudden death. *Brain Dev* 1992; 14: 309–14.
3. Murphy JV, *et al.* Deaths in young children receiving nitrazepam. *J Pediatr* 1987; 111: 145–7.
4. Rintahaka PJ, *et al.* Incidence of death in patients with intractable epilepsy during nitrazepam treatment. *Epilepsia* 1999; 40: 492–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nitrazepam as probably porphyrinogenic; it should be prescribed only for compelling indications and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Nitrazepam is fairly readily absorbed from the gastrointestinal tract, although there is some individual variation. Peak plasma concentrations occur 2 to 3 hours after ingestion. It is about 87% bound to plasma proteins. It crosses the blood-brain and the placental barriers and traces are found in breast milk. Nitrazepam is metabolised in the liver, mainly by nitroreduction followed by acetylation; none of the metabolites possess significant activity. It is excreted in the urine in the form of its metabolites (free or conjugated) with only small amounts of a dose appearing unchanged. Up to about 20% of an oral dose is found in the faeces. Mean elimination half-lives of 24 to 30 hours have been reported.

Distribution into breast milk. A mean milk-to-plasma ratio of 0.27 was obtained after giving nitrazepam 5 mg orally for 5 nights to 9 puerperal women.[1] The accumulation of nitrazepam in milk over the study period was similar to that in plasma.

1. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; 30: 787–93.

Hepatic impairment. The pharmacokinetics of intravenous nitrazepam in 12 patients with cirrhosis of the liver has been compared with 9 healthy subjects aged 22 to 49 years and 8 healthy elderly subjects aged 67 to 76 years.[1] The mean elimination half-life of nitrazepam was 26 hours in young and 38 hours in elderly subjects, the difference, which was not significant, being chiefly due to the greater volume of distribution in elderly subjects. Although there was also no significant difference between young and elderly subjects in percentage of unbound nitrazepam (13.0 and 13.9% respectively) there was a substantially higher unbound fraction in the patients with cirrhosis, the mean value being 18.9%, and clearance of unbound nitrazepam was reduced relative to healthy subjects.

1. Jochemsen R, *et al.* Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. *Br J Clin Pharmacol* 1983; 15: 295–302.

Metabolism. Although the acetylation of the reduced metabolite of nitrazepam has been reported to be controlled by acetylator phenotype,[1] no significant differences between either half-life or residual effects of nitrazepam were seen in slow and fast acetylators.[2]

1. Karim AKMB, Price Evans DA. Polymorphic acetylation of nitrazepam. *J Med Genet* 1976; 13: 17–19.
2. Swift CG, *et al.* Acetylator phenotype, nitrazepam plasma concentrations and residual effects. *Br J Clin Pharmacol* 1980; 9: 312P–313P.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Alodorm; Mogadon; *Austria*: Mogadon; *Belg.*: Mogadon; *Braz.*: Nitrapan; Nitrazepol; Sonebon; *Canad.*: Mogadon; Nitrazadon; *Denm.*: Apodorm; Mogadon†; Pacisyn; *Fin.*: Insomin; *Fr.*: Mogadon; *Ger.*: Dormo-Puren†; Imeson; Mogadan; Novanox; Radedorm†; *Hong Kong*: Alodorm†; Mogadon; *Hung.*: Eunoctin; *India*: Baronite; Dormin; Gentravit; Hypnoril; Hypnotex; Insomin; Nigap; Nipam; Nitavan; Nithra; Nitravet; Nitraz; Nitrocalm; Nitrosun; Nitrosym; *Indon.*: Dumolid; *Irl.*: Mogadon; *Israel*: Numbon; *Ital.*: Mogadon; *Neth.*: Mogadon; *Norw.*: Apodorm; Mogadon; *NZ*: Insoma†; Nitrados; *Philipp.*: Mozepam; *Rus.*: Eunoctin (Эунокгин); Nitrosun (Нитросан); Radedorm (Радедорм); *S.Afr.*: Arem; Mogadon; Ormodon†; Paxadorm; *Singapore*: Dima†; Nitrados; *Swed.*: Apodorm†; Mogadon; *Switz.*: Mogadon; *Thai.*: Nitrados; *UK*: Mogadon; Remnos; Somnite†; *Venez.*: Onirema.

Multi-ingredient Preparations. *China*: Xi Li Shu (希力舒).

Pharmacopoeial Preparations

BP 2014: Nitrazepam Oral Suspension; Nitrazepam Tablets.

Nordazepam *(rINN)*

A-101; Demethyldiazepam; Desmethyldiazepam; *N*-Desmethyldiazepam; Nordazépam; Nordazepamum; Nordiazepam; Ro-5-2180; Нордазепам.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{11}ClN_2O$=270.7

CAS — 1088-11-5.

ATC — N05BA16.

ATC Vet — QN05BA16.

UNII — 67220MCM01.

Profile

Nordazepam is a long-acting benzodiazepine with the general properties of diazepam (p. 1063.2). It is the principal active metabolite of several benzodiazepines and has a half-life of 2 to 5 days. It is given in oral doses of up to 15 mg daily for the short-term treatment of anxiety disorders (p. 1028.1) and insomnia (p. 1033.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Calmday; *Fr.*: Nordaz; *Ger.*: Tranxilium N†; *Gr.*: Lomax; *Ital.*: Madar; *Singapore*: Nordaz.

Olanzapine *(BAN, USAN, rINN)*

LY-170053; Olantsapiini; Olanzapin; Olanzapina; Olanzapinum; Олансапин.

2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine.

$C_{17}H_{20}N_4S$=312.4

CAS — 132539-06-1.

ATC — N05AH03.

ATC Vet — QN05AH03.
UNII — N7U69T4SZR.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Olanzapine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. It shows polymorphism.

USP 36: (Olanzapine). A yellow crystalline solid. Practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; soluble in propyl alcohol; sparingly soluble in acetonitrile.

Stability. A suspension of olanzapine 1 mg/mL, made by crushing olanzapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for 2 weeks when stored in a refrigerator.[1]

1. Harvey EJ, *et al.* The preparation and stability of a liquid olanzapine preparation for oral administration in hospitals. *Pharm J* 2000; 265: 275–6.

Olanzapine Embonate *(BANM, rINNM)*

Embonato de olanzapina; Olanzapine, Embonate d'; Olanzapine Pamoate (USAN); Olanzapini Embonas; Оланзапина Эмбонат.

$C_{23}H_{16}O_6.C_{17}H_{20}N_4S.H_2O$=718.8

CAS — 221373-18-8.
ATC — N05AH03.
ATC Vet — QN05AH03.
UNII — X7S6Q4MHCB.

Uses and Administration

Olanzapine is a thienobenzodiazepine atypical antipsychotic. It has affinity for serotonin, muscarinic, histamine (H_1), and adrenergic (α_1) receptors as well as various dopamine receptors.

Olanzapine is used for the management of schizophrenia (below) and for the treatment of moderate to severe mania associated with bipolar disorder (below). It is also given with fluoxetine for the treatment of the depressive phase of bipolar disorder (below) and for treatment-resistant unipolar depression (p. 398.1). Olanzapine is usually given orally or by intramuscular injection as the base. The longer-acting embonate salt is given by intramuscular injection. For all routes, doses are expressed in terms of the equivalent amount of olanzapine; olanzapine embonate 230.1 mg is equivalent to about 100 mg of olanzapine.

UK licensed product information states that the usual initial oral dose for **schizophrenia** is 10 mg daily as a single dose; thereafter dose adjustments may be made according to response at intervals of not less than 24 hours to within the range of 5 to 20 mg daily. The licensed starting dose in the USA is 5 to 10 mg daily and it is recommended that dosage adjustments beyond 10 mg daily are made at intervals of not less than 1 week; the daily dosage should be adjusted in steps of 5 mg.

The long-acting depot preparation may also be given by deep intramuscular injection every 2 or 4 weeks for maintenance therapy of schizophrenia. Patients with no history of olanzapine use should initially be treated with olanzapine orally to assess tolerability and response. Treatment may then be started as follows, according to target oral olanzapine dose:

- 10 mg daily: 210 mg every 2 weeks or 405 mg every 4 weeks, then 150 mg every 2 weeks or 300 mg every 4 weeks after 2 months of therapy
- 15 mg daily: 300 mg every 2 weeks, then 210 mg every 2 weeks or 405 mg every 4 weeks after 2 months of therapy
- 20 mg daily: 300 mg every 2 weeks, then 300 mg every 2 weeks after 2 months of therapy

Patients should be monitored for signs of relapse during the first 1 or 2 months of treatment. If oral olanzapine supplementation is required, then the combined total dose of both formulations should not exceed the corresponding maximum oral dose of 20 mg daily.

For the treatment of *acute mixed or manic episodes* in **bipolar disorder**, a recommended initial oral dose is 10 or 15 mg daily as monotherapy or 10 mg if given as an adjunct to lithium or valproate; the daily dosage may be adjusted in steps of 5 mg if necessary, at intervals of not less than 24 hours to a dose of between 5 and 20 mg daily. If a response is achieved, therapy may continue at the same dosage to prevent recurrence. For *maintenance treatment* in patients whose manic episodes have responded previously to olanzapine, the recommended starting dose is 10 mg daily.

For the treatment of the **depressive phase** of bipolar disorder and for treatment-resistant **unipolar depression**, a recommended initial oral dose of olanzapine is 5 mg once daily; dosage adjustments may be made according to efficacy and tolerance to within the range of olanzapine 5 to 12.5 mg daily for bipolar disorder or 5 to 20 mg daily for unipolar depression. In some countries olanzapine is available as a fixed-dose combination with fluoxetine for these indications.

For the **rapid control of agitation and disturbed behaviour** in patients with schizophrenia or mania, olanzapine may be given intramuscularly in an initial dose of 5 to 10 mg followed by 5 to 10 mg as required after 2 hours. Not more than 3 injections should be given in any 24-hour period and the maximum daily dose, including olanzapine given orally, should not exceed 20 mg. Injections may be given for a maximum of 3 days but transfer to oral therapy should be started as soon as possible.

The metabolism of olanzapine might be slower in female, elderly, or non-smoking patients; if more than one of these factors is present, a lower initial dose (e.g. 5 mg daily if given orally) and a more gradual dose escalation should be considered. The intramuscular dose should be reduced by half in the elderly. A lower starting dose of 150 mg every 4 weeks of the long-acting depot preparation is not routinely indicated but should be considered in patients aged over 65 years; treatment should not be started in those aged over 75 years due to lack of data. See Administration in Hepatic or Renal Impairment, below for doses in patients with hepatic or renal impairment.

For details of uses and associated doses in adolescents, see Administration in Children, below.

The benzoate and tartrate salts are used similarly in some countries.

Administration in children. In the USA, olanzapine is licensed for the treatment of schizophrenia and as monotherapy for acute manic or mixed episodes associated with bipolar disorder in adolescents aged 13 to 17 years. For both indications, the recommended initial oral dose is 2.5 or 5 mg once daily, increased to the target dose of 10 mg daily. Efficacy has been shown with doses ranging from 2.5 to 20 mg daily. Dosage adjustments, if necessary, should be made in steps of 2.5 or 5 mg.

Although unlicensed in the UK for use in children and adolescents aged under 18 years, the *BNFC* suggests that olanzapine may be given to those aged 12 years and over. For the management of schizophrenia and the treatment of mania as part of combination therapy, an initial oral dose of 5 to 10 mg daily, adjusted to the usual range of 5 to 20 mg daily, may be given; for the treatment of mania as monotherapy, an initial oral dose of 15 mg daily, adjusted to the usual range of 5 to 20 mg daily, is suggested.

Administration in hepatic or renal impairment. A starting dose of 5 mg daily of olanzapine orally or by intramuscular injection, or 150 mg every 4 weeks of the long-acting depot preparation, may be necessary for patients with renal or hepatic impairment; for patients with moderate hepatic insufficiency (Child-Pugh classes A and B), the starting dose should only be increased with caution.

Bipolar disorder. Olanzapine is of benefit for the treatment, and prevention, of mania, with or without psychosis, in patients with bipolar disorder (p. 397.2), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of olanzapine-induced mania (see p. 1091.3).

There is also increasing interest in the use of olanzapine for the depressive phase of bipolar disorder, and for other forms of resistant depression. In some countries olanzapine is available as a fixed-dose combination with fluoxetine.

References.

1. Shelton RC, *et al.* A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001; 158: 131–4.
2. Rendell JM, *et al.* Olanzapine alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/05/05).
3. McCormack PL, Wiseman LR. Olanzapine: a review of its use in the management of bipolar I disorder. *Drugs* 2004; 64: 2709–26.
4. Shelton RC. Olanzapine/fluoxetine combination for bipolar depression. *Expert Rev Neurother* 2006; 6: 33–9.
5. Tohen M, *et al.* Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry* 2007; 164: 1547–56.
6. Strawn JR, Delbello MP. Olanzapine for the treatment of bipolar disorder in children and adolescents. *Expert Opin Pharmacother* 2008; 9: 467–74.
7. Deeks ED, Keating GM. Olanzapine/fluoxetine: a review of its use in the treatment of acute bipolar depression. *Drugs* 2008; 68: 1115–37.
8. Cipriani A, *et al.* Olanzapine in long-term treatment for bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 01/06/09).
9. Trivedi MR, *et al.* An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry* 2009; 70: 387–96.

Nausea and vomiting. For mention of the use of olanzapine as a second-line drug to control nausea and vomiting in palliative care see p. 1814.3.

Parkinsonism. Olanzapine is associated with a relatively low incidence of extrapyramidal disorders and has been studied[1] for use in the treatment of psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p. 1030.2). However, there have been several reports of adverse effects including exacerbation of the movement disorder (see Parkinsonism, under Precautions, p. 1092.1)

1. Wolters EC, *et al.* Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. *Neurology* 1996; 47: 1085–7.

Psychiatric disorders. The main treatment for *post-traumatic stress disorder* (p. 1029.2) is psychotherapy but adjunctive olanzapine may be used in patients refractory to psychotherapy and/or drug treatment with antidepressants. Olanzapine has also been tried for the control of *aggression* in children with autism and conduct disorder (see Disturbed Behaviour, p. 1030.2).

Schizophrenia. Studies suggest that olanzapine is as effective as haloperidol against positive symptoms of schizophrenia (p. 1031.3) and more effective against negative symptoms in the short-term and possibly in the long term,[1-5] although a systematic review considered the evidence equivocal.[6] Quality of life has also been judged to be greater in patients treated with olanzapine.[7] In comparative studies, extrapyramidal adverse effects have been less frequent with olanzapine than haloperidol and fewer patients have discontinued treatment with olanzapine. There are relatively few published comparisons with other atypical antipsychotics, but one systematic review[8] concluded that there was little to differentiate between olanzapine and risperidone apart from their adverse effects; risperidone was particularly associated with movement disorders and sexual dysfunction while olanzapine induced rapid weight gain. Another study has suggested that olanzapine is not inferior to clozapine.[9] A more recent systematic review[10] found that olanzapine may be slightly more effective than aripiprazole, quetiapine, risperidone and ziprasidone, whereas no difference in efficacy was found when compared with amisulpride and clozapine. Olanzapine was also found to be associated with more weight gain than most other atypical antipsychotics except for clozapine. Olanzapine's efficacy in the treatment of patients with refractory schizophrenia remains to be determined; a small, randomised study found it to be no more effective than haloperidol.[11]

Olanzapine has also been studied[12-14] for the treatment of schizophrenia in children and adolescents, and is licensed for such use in some countries.

1. Beasley CM, *et al.* Olanzapine HGAD Study Group. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996; 14: 111–23.
2. Beasley C, *et al.* Olanzapine versus haloperidol: long-term results of the multi-center international trial. *Eur Neuropsychopharmacol* 1996; 6 (suppl 3): 59.
3. Beasley CM, *et al.* Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* 1997; 7: 125–37.
4. Tollefson GD, *et al.* Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997; 154: 457–65.
5. Bhana N, *et al.* Olanzapine: an updated review of its use in the management of schizophrenia. *Drugs* 2001; 61: 111–61.
6. Duggan L, *et al.* Olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 24/05/05).
7. Hamilton SH, *et al.* Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology* 1998; 18: 41–9.
8. Jayaram MB, *et al.* Risperidone versus olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 16/01/07).
9. Naber D, *et al.* Randomized double blind comparison of olanzapine vs clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatr Scand* 2005; 111: 106–15.
10. Komossa K, *et al.* Olanzapine versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 24/03/10).
11. Buchanan RW, *et al.* Olanzapine treatment of residual positive and negative symptoms. *Am J Psychiatry* 2005; 162: 124–9.
12. Quintana H, *et al.* An open-label study of olanzapine in children and adolescents with schizophrenia. *J Psychiatr Pract* 2007; 13: 86–96.
13. Dittmann RW, *et al.* Effectiveness and tolerability of olanzapine in the treatment of adolescents with schizophrenia and related psychotic disorders: results from a large, prospective, open-label study. *J Child Adolesc Psychopharmacol* 2008; 18: 54–69.
14. Kryzhanovskaya L, *et al.* Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2009; 48: 60–70.

Stuttering. Although olanzapine may be of benefit in the treatment of stuttering (p. 1078.1),[1,2] it has been associated with reports of stuttering in 6 adult patients with schizophrenia or depression.[3]

1. Lavid N, *et al.* Management of child and adolescent stuttering with olanzapine: three case reports. *Ann Clin Psychiatry* 1999; 11: 233–6.
2. Maguire GA, *et al.* Olanzapine in the treatment of developmental stuttering: a double-blind, placebo-controlled trial. *Ann Clin Psychiatry* 2004; 16: 63–7.
3. Bär KJ, *et al.* Olanzapine- and clozapine-induced stuttering: a case series. *Pharmacopsychiatry* 2004; 37: 131–4.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) haloperidol or pimozide are com-

monly used but atypical antipsychotics, including olanzapine, are increasingly being tried.[1-5]

1. Stamenkovic M, *et al.* Effective open-label treatment of tourette's disorder with olanzapine. *Int Clin Psychopharmacol* 2000; 15: 23–8.
2. Onofrj M, *et al.* Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. *J Neurol* 2000; 247: 443–6.
3. Budman CL, *et al.* An open-label study of the treatment efficacy of olanzapine for Tourette's disorder. *J Clin Psychiatry* 2001; 62: 290–4.
4. Stephens RJ, *et al.* Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome: a pilot study. *J Child Adolesc Psychopharmacol* 2004; 14: 255–66.
5. McCracken JT, *et al.* Effectiveness and tolerability of open label olanzapine in children and adolescents with Tourette syndrome. *J Child Adolesc Psychopharmacol* 2008; 18: 501–8.

Adverse Effects, Treatment, and Precautions

Although olanzapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with olanzapine are somnolence and weight gain; hyperprolactinaemia is also common, but usually asymptomatic. Increased appetite, dizziness, fatigue, elevated plasma glucose, triglyceride, and liver enzyme values, oedema, orthostatic hypotension, and mild transient antimuscarinic effects such as constipation and dry mouth are also relatively common. Blood dyscrasias including agranulocytosis, eosinophilia, leucopenia, neutropenia, and thrombocytopenia have also been reported. Weight gain, sedation, and liver enzyme values, lipid, and prolactin alterations may be greater in adolescents than in adults. More severe abnormalities of glucose homoeostasis are uncommon; severe hyperglycaemia, or exacerbation of pre-existing diabetes, sometimes leading to ketoacidosis, coma, or death, has occurred. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Clinical monitoring of plasma lipids and weight have also been recommended.

Olanzapine is associated with a low incidence of extrapyramidal effects, including tardive dyskinesia, although these effects may be more likely at high doses and in the elderly; the risk of tardive dyskinesia also increases with long-term use. Neuroleptic malignant syndrome has been reported rarely.

Patients receiving olanzapine intramuscularly should be closely observed for 2 to 4 hours for hypotension, bradyarrhythmia, and hypoventilation. Olanzapine should not be given intramuscularly to patients with a history of cardiovascular disease or after heart surgery; caution is recommended when giving olanzapine orally to such patients and to those with cerebrovascular disease or conditions predisposing to hypotension. It is recommended that blood pressure is periodically assessed in elderly patients.

The antimuscarinic effects of olanzapine contra-indicate its use in patients with angle-closure glaucoma; caution is also advised in those with conditions such as benign prostatic hyperplasia or paralytic ileus. Olanzapine is also not recommended in Parkinson's disease since its use has commonly been associated with an increase in parkinsonian symptoms and hallucinations. It should be used with caution in patients with hepatic impairment, or a history of blood dyscrasias, bone marrow depression, or myeloproliferative disease. Seizures are rare with olanzapine but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

When olanzapine is used for the depressive phase in bipolar disorder or for unipolar depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see Bipolar Disorder, p. 397.2 and Depression, p. 398.1.

Olanzapine may affect the performance of skilled tasks such as driving.

Withdrawal symptoms, including sweating, tremor, anxiety, and nausea and vomiting, have occurred rarely when olanzapine has been stopped abruptly; a gradual dose reduction may be appropriate when stopping olanzapine.

References.

1. Beasley CM, *et al.* Safety of olanzapine. *J Clin Psychiatry* 1997; 58 (suppl 10): 13–17.
2. Biswas PN, *et al.* The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. *J Psychopharmacol* 2001; 15: 265–71.
3. Kryzhanovskaya LA, *et al.* The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials. *J Clin Psychiatry* 2009; 70: 247–58. Correction. *ibid.*; 1729.
4. Marder SR, *et al.* Case reports of postmarketing adverse event experiences with olanzapine intramuscular treatment in patients with agitation. *J Clin Psychiatry* 2010; 71: 433–41.

Breast feeding. From a study[1] of the distribution of olanzapine into breast milk in 7 breast feeding women taking a median dose of 7.5 mg daily, it was estimated that the weight-adjusted median dose ingested by the breast-fed infants was 1.02% of the maternal dose. Olanzapine was not detected in the plasma of the 6 infants from whom a sample was taken; no adverse effects were seen in any of the 7 infants. However, UK licensed product information states that at steady state the estimated mean exposure of breast-fed infants of mothers taking olanzapine would be 1.8% of the maternal dose and recommends that patients should not breast feed if they are taking olanzapine.

1. Gardiner SJ, *et al.* Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. *Am J Psychiatry* 2003; 160: 1428–31.

Effects on the blood. A review[1] has described 11 reports of olanzapine-associated haematotoxicity that included 3 cases of agranulocytosis, 6 of neutropenia, and 2 of leucopenia. In most cases, the haematotoxicity developed within the first month of treatment and patients recovered after olanzapine withdrawal. There was a history of clozapine-associated haematotoxicity in 5 patients. It was suggested that white blood cell counts should be monitored periodically during olanzapine treatment.

Olanzapine has also apparently delayed recovery of granulocyte counts in patients with clozapine-induced granulocytopenia who were switched to olanzapine before blood counts had returned to the normal range.[2]

There have been case reports[3,4] of thrombocytopenia associated with olanzapine treatment. In one report,[3] the patient improved on stopping olanzapine but subsequently had a similar episode associated with benzatropine therapy. In another report,[4] an elderly patient with pre-existing immune thrombocytopenia died from bleeding complications due to thrombocytopenia associated with olanzapine treatment; the patient's plasma concentration of olanzapine was reported to be 10 times the usual mean therapeutic value.

1. Tolosa-Vilella C, *et al.* Olanzapine-induced agranulocytosis: a case report and review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26: 411–4.
2. Flynn SW, *et al.* Prolongation of clozapine-induced granulocytopenia associated with olanzapine. *J Clin Psychopharmacol* 1997; 17: 494–5.
3. Bogunovic O, Viswanathan R. Thrombocytopenia possibly associated with olanzapine and subsequently with benztropine mesylate. *Psychosomatics* 2000; 41: 277–88.
4. Carrillo JA, *et al.* Thrombocytopenia and fatality associated with olanzapine. *Eur J Clin Pharmacol* 2004; 60: 295–6.

Effects on body temperature. Olanzapine has been associated with occasional reports of hypothermia. In one report[1] body temperature fell as low as 33.4 degrees over several days in a woman receiving olanzapine for bipolar disorder. The patient, who also had subclinical hypothyroidism, was asymptomatic, and body temperature returned to normal once olanzapine was stopped; it was unclear whether the endocrine abnormalities had contributed to the condition.

1. Blass DM, Chuen M. Olanzapine-associated hypothermia. *Psychosomatics* 2004; 45: 135–9.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.

1. Haberfellner EM, Rittmannsberger H. Weight gain during long-term treatment with olanzapine: a case series. *Int Clin Psychopharmacol* 2004; 19: 251–3.
2. Hennen J, *et al.* Weight gain during treatment of bipolar I patients with olanzapine. *J Clin Psychiatry* 2004; 65: 1679–87.
3. Hester EK, Thrower MR. Current options in the management of olanzapine-associated weight gain. *Ann Pharmacother* 2005; 39: 302–10.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Further references for such effects associated with olanzapine use are given below; in some cases the outcome was fatal.

1. Bettinger TL, *et al.* Olanzapine-induced glucose dysregulation. *Ann Pharmacother* 2000; 34: 865–7.
2. Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycemic nonketonic coma. *Ann Pharmacother* 2001;35: 300–302.
3. Bonanno DG, *et al.* Olanzapine-induced diabetes mellitus. *Ann Pharmacother* 2001; 35: 563–5.
4. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother* 2001; 35: 1556–8.
5. Koller E, *et al.* Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA* 2001; 286: 2547–8.
6. CSM. Olanzapine (Zyprexa) and diabetes. *Current Problems* 2002; 28: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074546&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
7. Koro CE, *et al.* Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002; 325: 243–5.
8. Ramaswamy K, *et al.* Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; 30: 589–99.

Effects on the cardiovascular system. Two of 3 elderly patients who developed venous thromboembolism shortly after starting treatment with olanzapine also had symptoms of pulmonary embolism.[1] There have been 2 further isolated cases[2,3] of pulmonary embolism associated with olanzapine therapy; it had been reported in a 28-year-old man[2] and in a 22-year-old man[3] after 10 weeks and after 6 months of olanzapine therapy, respectively. Both patients recovered and were switched to another atypical antipsychotic.

For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

1. Hägg S, *et al.* Olanzapine and venous thromboembolism. *Int Clin Psychopharmacol* 2003; 18: 299–300.
2. Waage IM, Gedde-Dahl A. Pulmonary embolism possibly associated with olanzapine treatment. *BMJ* 2003; 327: 1384.
3. Health Canada. Olanzapine (Zyprexa): suspected association with pulmonary embolism. *Can Adverse React News* 2005; 15 (1): 5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n1-eng.pdf (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

Further references.

1. Osser DN, *et al.* Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry* 1999; 60: 767–70.

Effects on the liver. Acute hepatocellular cholestatic jaundice developed in a 78-year-old woman 13 days after starting treatment with olanzapine.[1]

1. Jadallah KA, *et al.* Acute hepatocellular-cholestatic liver injury after olanzapine therapy. *Ann Intern Med* 2003; 138: 357–8.

Effects on the nervous system. A 31-year-old woman with a complicated medical history suffered three generalised tonic-clonic seizures after 13 days of therapy with olanzapine.[1] She recovered after treatment with phenytoin. Another patient with Huntington's disease also suffered a severe generalised tonic-clonic seizure after treatment with olanzapine 30 mg daily for 1 month.[2] Olanzapine was continued but carbamazepine was added; there was no recurrence of the seizure.

1. Lee JW, *et al.* Seizure associated with olanzapine. *Ann Pharmacother* 1999; 33: 554–6.
2. Bonelli RM. Olanzapine-associated seizure. *Ann Pharmacother* 2003; 37: 149–50.

Effects on the pancreas. There have been reports of pancreatitis associated with olanzapine.[1-3] See also under Clozapine, p. 1060.2.

1. Doucette DE, *et al.* Olanzapine-induced acute pancreatitis. *Ann Pharmacother* 2000; 34: 1128–31.
2. Hagger R, *et al.* Olanzapine and pancreatitis. *Br J Psychiatry* 2000; 177: 567.
3. Waage C, *et al.* Olanzapine-induced pancreatitis: a case report. *JOP* 2004; 5: 388–91.

Effects on sexual function. Priapism has been reported[1,2] in 2 patients receiving olanzapine.

1. Deirmenjian JM, *et al.* Olanzapine-induced reversible priapism: a case report. *J Clin Psychopharmacol* 1998; 18: 351–3.
2. Songer DA, Barclay JC. Olanzapine-induced priapism. *Am J Psychiatry* 2001; 158: 2087–8.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Extrapyramidal disorders. There have been isolated reports[1,2] of tardive dyskinesia associated with olanzapine treatment. However, the incidence of extrapyramidal effects (p. 1049.2) is generally lower with atypical than classical antipsychotics.

1. Herrán A, Vázquez-Barquero JL. Tardive dyskinesia associated with olanzapine. *Ann Intern Med* 1999; 131: 72.
2. Bella VL, Piccoli F. Olanzepine-induced tardive dyskinesia. *Br J Psychiatry* 2003; 182: 81–2.

Mania. Although olanzapine is used in the treatment of bipolar disorder, it has been associated with reports of mania in both schizophrenic and bipolar patients.[1-4] A report sponsored by the manufacturers noted that no association was seen in pooled data from 2 placebo-controlled studies involving 254 bipolar patients.[5]

1. Lindenmayer J-P, Kiebanov R. Olanzapine-induced manic-like syndrome. *J Clin Psychiatry* 1998; 59: 318–19.
2. Fitz-Gerald MJ, *et al.* Olanzapine-induced mania. *Am J Psychiatry* 1999; 156: 1114.
3. Aubry J-M, *et al.* Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; 61: 649–55.
4. Henry C, Demotes-Mainard J. Olanzapine-induced mania in bipolar disorders. *J Psychiatry Neurosci* 2002; 27: 200–201.
5. Baker RW, *et al.* Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *J Affect Disord* 2003; 73: 147–53.

Neuroleptic malignant syndrome. Cases of neuroleptic malignant syndrome (p. 1050.2) have been associated with olanzapine therapy.[1-4]

1. Filice GA, *et al.* Neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 1998; 32: 1158–9.

2. Nyfort-Hansen K, Alderman CP. Possible neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 2000; 34: 667.
3. Suh H, *et al.* Neuroleptic malignant syndrome and low-dose olanzapine. *Am J Psychiatry* 2003; 160: 796.
4. Kogoj A, Velikonja L. Olanzapine induced neuroleptic malignant syndrome–a case review. *Hum Psychopharmacol* 2003; 18: 301–9.

Overdosage. A 2½-year-old boy was found sleeping and difficult to arouse after taking one or two 7.5-mg olanzapine tablets.[1] His reported symptoms included agitation, aggressive behaviour, miosis, hypersalivation, tachycardia, and ataxia; he recovered after 24 hours. Symptoms suggestive of diabetes insipidus, together with mild CNS depression, have also been reported,[2] in an adolescent who took 75 mg of olanzapine with a small quantity of prazepam. The polyuria responded to desmopressin. A review[3] identified 29 fatalities associated with olanzapine overdose, but evidence of a direct causative relationship was limited.

1. Yip L, *et al.* Olanzapine toxicity in a toddler. *Pediatrics* 1998; 102: 1494.
2. Etienne L, *et al.* Polyuria after olanzapine overdose. *Am J Psychiatry* 2004; 161: 1130.
3. Chue P, Singer P. A review of olanzapine-associated toxicity and fatality in overdose. *J Psychiatry Neurosci* 2003; 28: 253–61.

Parkinsonism. Worsening of motor function has been reported[1-4] in patients with parkinsonism after use of olanzapine.

1. Graham JM, *et al.* Olanzapine in the treatment of hallucinosis in idiopathic Parkinson's disease: a cautionary note. *J Neurol Neurosurg Psychiatry* 1998 65: 774–7.
2. Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine. *Mov Disord* 1999; 14: 1014–16.
3. Goetz CG, *et al.* Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* 2000; 55: 789–94.
4. Manson AJ, *et al.* Low-dose olanzapine for levodopa induced dyskinesias. *Neurology* 2000; 55: 795–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies olanzapine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The manufacturer has reviewed both prospective and retrospective cases of pregnancies that have been exposed to olanzapine treatment.[1] Of the 37 prospective pregnancies, there were 14 therapeutic abortions (with no reported abnormality in the fetus), 3 spontaneous abortions (again with no reported abnormality in the fetus), and 1 still-birth. The remaining 19 pregnancies included 16 normal births without complications and 1 premature birth; the 2 other births were complicated by post-term deliveries. Eleven retrospective cases were also identified and included 2 cases of major malformation (dysplastic kidney and Down's syndrome), 1 case of fetal death after a maternal overdose, and 1 case each of neonatal convulsion and sudden infant death. For comments on the use of some atypical antipsychotics, including olanzapine, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

1. Goldstein DJ, *et al.* Olanzapine-exposed pregnancies and lactation: early experience. *J Clin Psychopharmacol* 2000; 20: 399–403.

Speech disorders. Although olanzapine may be used in the treatment of stuttering, it has also been associated with reports of the development of the disorder, see under Uses and Administration, p. 1090.3.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by olanzapine. Olanzapine may antagonise the effects of dopaminergics. Neutropenia may be more common when olanzapine is given with valproate. Use with valproate or lithium has also been associated with an increased incidence of tremor, dry mouth, increased appetite, and weight gain. There may be a risk of QT prolongation when olanzapine is given with other drugs that are known to cause this effect.

Drugs that induce hypotension, bradycardia, or respiratory depression should be used with caution in patients given intramuscular olanzapine. Parenteral benzodiazepine treatment should be given at least 1 hour after intramuscular olanzapine as it is recommended that they are not given together.

The metabolism of olanzapine is mediated to some extent by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit, induce, or act as a substrate to this isoenzyme may affect plasma concentrations of olanzapine and a dose adjustment of olanzapine may be required. The CYP1A2 inhibitor fluvoxamine significantly inhibits the metabolism of olanzapine. The clearance of olanzapine is increased by tobacco smoking and carbamazepine.

Valproate. In a study of 4 patients, valproate reduced plasma concentrations of olanzapine by 32.3 to 78.8% (mean 53.6%).[1]

1. Bergemann N, *et al.* Valproate lowers plasma concentrations of olanzapine. *Pharmacopsychiatry* 2005; 38: 44.

Pharmacokinetics

Olanzapine is well absorbed from the gastrointestinal tract after oral doses but undergoes considerable first-pass metabolism. Peak plasma concentrations occur about 5 to 8 hours after oral doses and about 15 to 45 minutes after an intramuscular dose. Olanzapine is about 93% bound to plasma proteins. It is extensively metabolised in the liver, mainly by direct glucuronidation and by oxidation mediated through the cytochrome P450 isoenzymes CYP1A2, and, to a lesser extent, CYP2D6. The 2 major metabolites, 10-*N*-glucuronide and 4'-*N*-desmethyl olanzapine, appear to be inactive. About 57% of a dose is excreted in the urine, mainly as metabolites, and about 30% appears in the faeces. The mean plasma elimination half-life has been variously reported to be about 30 to 38 hours; half-lives tend to be longer in female than in male patients. Olanzapine is distributed into breast milk.

References.

1. Callaghan JT, *et al.* Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999; 37: 177–93.
2. Markowitz JS, *et al.* Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol* 2006; 46: 164–71.
3. Bigos KL, *et al.* Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol* 2008; 48: 157–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Apsico; Midax; Sartina; Simina; Zyprexa; ***Austral.***: Lanzek; Lanzek; Zylap; Zypine; Zyprexa; ***Austria***: Zypadhera; Zyprexa; ***Belg.***: Zypadhera; Zyprexa; ***Braz.***: Lanzamed; Olazofren; Zopix; Zyprexa; ***Canad.***: Zyprexa; ***Chile***: Amulsin; Oleanz; Olivin; Sincris; Tanssel; Zapinex; Zyprexa; ***China***: Ou Lan Ning (欧兰宁); Ximin (悉敏); Zyprexa (再普乐); ***Cz.***: Aedon; Arkolamyl; Clingozan; Lapozan; Nykob; Olazax; Olipazix; Olpinat; Parnassan; Stygapon; Zalasta; Zolafren; Zypadhera; Zyprexa; ***Denm.***: Arkolamyl; Asterilon†; Kynapine; Lazapix; Nykob; Nylsanuc; Olzamed†; Zalasta; Zamil; Zynilmed†; Zypadhera; Zyprexa; ***Fin.***: Solazin†; Zyprexa; ***Fr.***: Arkolamyl; Zypadhera; Zyprexa; ***Ger.***: Zalasta; Zypadhera; Zyprexa; ***Gr.***: Bloonis; Caprilon; Lapenza; Lapozan; Lazap; Niolib; Norpen Oro; Nyzol; Olanzalet; Olapine; Olenxa; Olmyzem; Ozapex; Xoltiva; Zalasta; Zalepin; Zonapin; Zoxil; Zypadhera; Zypefar; Zyprexa; ***Hong Kong***: Zyprexa; ***Hung.***: Bloonis; Mitab; Olanzep; Olpinat; Parnassan; Zypadhera; Zyprexa; ***India***: Cinol; Dopin; Jolyon-MD; Joyzol; Lano; Lanopin; M-Olan; Manza; Meltolan; Olace; Oladay; Olan; Olandus; Olanex; Olanzapik; Olapax; Olapin; Oleanz; Oles; Olexar; Olima; Oliza; Olpin; Oltal; Olzap; Onza; Opin; Opirap; Ozace; Ozap; Ozapin; Psycholanz; ***Indon.***: Olandoz; Remital; Zyprexa; ***Irl.***: Arkolamyl; Kozylex; Olazax; Rolyprexa; Zalasta; Zypadhera; Zyprexa; ***Israel***: Zappa; Zypadhera; Zyprexa; ***Ital.***: Arkolamyl; Olafid; Zyprexa; ***Jpn***: Zyprexa; ***Malaysia***: Zyprexa; ***Mex.***: Zyprexa; ***Neth.***: Arkolamyl; Clingozan†; Kozylex†; Lansyn; Lazapix†; Olanzaran; Olasyn; Olazax; Olstadryn†; Ozapex; Sanza; Synza; Zalasta; Zypadhera; Zyprexa; ***Norw.***: Zypadhera; Zyprexa; ***NZ***: Olanzine; Zyprexa; ***Philipp.***: Olan; Olanzapro; Zanprex; Zyprexa; ***Pol.***: Anzorin; Arkolamyl; Asterilon; Clingozan; Lanzapin; Nykob; Olanzin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Parnassan; Ranofren; Sanza; Synza; Zalasta; Zapilux; Zolafren; Zolaxa; Zypadhera; Zyprexa; ***Port.***: Decolan; Fordep†; Lernup; Nakozap†; Nolian†; Olan; Olapin†; Olasyn; Olazax; Synza; Tizina; Xapritx†; Zalasta; Ziprodec; Zolafren†; Zonapir†; Zypadhera; Zyprexa; ***Rus.***: Zalasta (Заласта); Zyprexa (Зипрекса); ***S.Afr.***: Oleanz; Olexar; Redilanz; Zyprexa; ***Singapore***: Onzapin; Zyprexa; ***Spain***: Arenbil; Zalasta; Zapris; Zolafren; Zypadhera; Zyprexa; ***Swed.***: Arkolamyl; Zalasta; Zypadhera; Zyprexa; ***Switz.***: Zyprexa; ***Thai.***: Olapin; Zyprexa; ***Turk.***: Apzet; Elynza; Oferta; Olfrex; Ollafax; Ozaprin; Rexapin; Zeprola; Zophix; Zyprexa; Zyzapin; ***UK***: Zypadhera; Zyprexa; ***Ukr.***: Zyprexa (Зипрекса); ***USA***: Zyprexa; ***Venez.***: Zyprexa.

Multi-ingredient Preparations. ***Chile***: Symbyax; ***India***: Cinol Forte; Cinol Plus; Depten-OZ; M-Olan Plus; Oladay-F; Olanex-F; Olapin Forte; Olapin Plus; Olorest-F; ***Mex.***: Symbyax; ***USA***: Symbyax.

Pharmacopoeial Preparations

USP 36: Olanzapine and Fluoxetine Capsules; Olanzapine Tablets.

Oxazepam *(BAN, USAN, rINN)*

Oksatsepaami; Oksazeoam; Oksazepam; Oksazepamas; Oxazepám; Oxazépam; Oxazepamum; Wy-3498; Оксазепам.

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one.

$C_{15}H_{11}ClN_2O_2$=286.7

CAS — 604-75-1.

ATC — N05BA04.

ATC Vet — QN05BA04.

UNII — 6GOW6DWN2A.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Oxazepam). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Oxazepam). A creamy-white to pale yellow, practically odourless powder. Practically insoluble in water; soluble 1 in 220 of alcohol, 1 in 270 of chloroform, and 1 in 2200 of ether. pH of a 2% suspension in water is between 4.8 and 7.0.

Uses and Administration

Oxazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used in the short-term management of anxiety disorders (p. 1028.1) and insomnia (p. 1033.2) associated with anxiety. Oxazepam is also used for the control of symptoms associated with alcohol withdrawal (p. 1735.1). Oxazepam is usually given as the base but the hemisuccinate has been used in some multi-ingredient preparations.

The usual oral dose of oxazepam for the treatment of anxiety or for control of symptoms of alcohol withdrawal is 15 to 30 mg three or four times daily. Lower doses of 7.5 to 15 mg three or four times daily may be tried for mild to moderate anxiety. A suggested initial dose for elderly or debilitated patients is 10 mg three times daily increased if necessary up to 10 to 20 mg three or four times daily. For the treatment of insomnia associated with anxiety oxazepam 15 to 25 mg may be given one hour before retiring; up to 50 mg may occasionally be necessary.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 10 mg of oxazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, but short-acting ones such as oxazepam may be preferred.

Seven patients with acute viral hepatitis, 6 with cirrhosis of the liver, and 16 age-matched healthy control subjects took a single dose of oxazepam 15 or 45 mg orally.[1] Urinary excretion rates and plasma elimination patterns were unaltered in patients with acute and chronic parenchymal liver disease. Oxazepam 15 mg orally was also given three times daily for 2 weeks to 2 healthy subjects and to 2 patients with cirrhosis and did not appear to accumulate in any of the four.

1. Shull HJ, *et al.* Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; 84: 420–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxazepam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/03/11)

Renal impairment. Pharmacokinetic studies suggest that, in general, the dosage of oxazepam does not need adjusting in patients with renal impairment.[1-3]

1. Murray TG, *et al.* Renal disease, age, and oxazepam kinetics. *Clin Pharmacol Ther* 1981; 30: 805–9.
2. Busch U, *et al.* Pharmacokinetics of oxazepam following multiple administration in volunteers and patients with chronic renal disease. *Arzneimittelforschung* 1981; 31: 1507–11.
3. Greenblatt DJ, *et al.* Multiple-dose kinetics and dialyzability of oxazepam in renal insufficiency. *Nephron* 1983; 34: 234–8.

Thyroid disorders. There was a reduction in half-life and an increase in the apparent oral clearance of oxazepam in 7 hyperthyroid patients.[1] In 6 hypothyroid patients there was no overall change in oxazepam elimination, although 5 of the 6 complained of drowsiness despite a relatively low dose (15 mg).

1. Scott AK, *et al.* Oxazepam pharmacokinetics in thyroid disease. *Br J Clin Pharmacol* 1984; 17: 49–53.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Oxazepam is well absorbed from the gastrointestinal tract; peak plasma concentrations occur about 2 to 3 hours after ingestion. It crosses the placenta and has been detected in breast milk. Oxazepam is about 97% bound to plasma

proteins and has been reported to have an elimination half-life ranging from about 4 to 15 hours. It is largely metabolised to the inactive glucuronide which is excreted in the urine.

Pregnancy. The placental passage of oxazepam and its metabolism in 12 women given a single dose of oxazepam 25 mg during labour has been studied.[1] Oxazepam was readily absorbed and peak plasma concentrations were in the same range as those reported in healthy males and non-pregnant females given the same dose, although the plasma half-life (range 5.3 to 7.8 hours in 8 subjects studied) was shorter than that reported for non-pregnant subjects. Oxazepam was detected in the umbilical vein of all 12 patients with the ratio between umbilical to maternal vein concentration of oxazepam reaching a value of about 1.35 and remaining constant beyond a dose-delivery time of 3 hours. All of the babies had a normal Apgar score value. The oxazepam plasma half-life in the newborns was about 3 to 4 times that of the mothers, although in 3 the plasma concentration of oxazepam conjugate rose during the first 6 to 10 hours after delivery indicating the ability of the neonate to conjugate oxazepam.

1. Tomson G, *et al.* Placental passage of oxazepam and its metabolism in mother and newborn. *Clin Pharmacol Ther* 1979; **25**: 74–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pausafren T; *Austral.*: Alepam; Murelax; Serepax; *Austria*: Adumbran; Anxiolit; Praxiten; *Belg.*: Seresta; Tranquo; *Canad.*: Novoxapam; *China*: Youfei (优菲); *Denm.*: Alopam; Oxabenz; Oxapax; *Fin.*: Opamox; Oxamin; *Fr.*: Seresta; *Ger.*: Adumbran†; Oxa; Praxiten; *Gr.*: Adumbran; *India*: Serepax; *Israel*: Vaben; *Ital.*: Limbial; Serpax; *Neth.*: Seresta; *Norw.*: Alopam; Sobril; *NZ*: Ox-Pam; *Pol.*: Oxam†; *Port.*: Serenal; *Rus.*: Nozepam (НОЗЕПАМ); Tazepam (Тазепам); *S.Afr.*: Medopam†; Noripam†; Purata; Serepax; *Swed.*: Oxascand; Sobril; *Switz.*: Anxiolit; Seresta; *USA*: Serax†.

Multi-ingredient Preparations. *Austria*: Anxiolit plus; *Chile*: Novalona; *Spain*: Suxidina; *Venez.*: Vuscobras.

Pharmacopoeial Preparations
BP 2014: Oxazepam Tablets;
USP 36: Oxazepam Capsules; Oxazepam Tablets.

Oxazolam *(rINN)*

Oxazolamum; Oxazolazepam; Оксазолам.
10-Chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.
$C_{18}H_{17}ClN_2O_2$=328.8
CAS — 24143-17-7.
UNII — 1V2WI2NA1C.

Pharmacopoeias. In *Jpn*.

Profile

Oxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been given orally in doses of 10 to 20 mg up to three times daily for the short-term treatment of anxiety disorders (p. 1028.1).

Oxazolam has also been given orally as a premedicant in general anaesthesia (p. 1899.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Nebusun†; Pelusarl; Serenal; Toccata†.

Paliperidone *(BAN, USAN, rINN)*

9-Hydroxyrisperidone; Paliperidona; Paliperidone; Paliperidonum; RO-76477; Палиперидон.
(±)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.
$C_{23}H_{27}FN_4O_3$=426.5
CAS — 144598-75-4.
ATC — N05AX13.
ATC Vet — QN05AX13.
UNII — 838F01T721.

Paliperidone Palmitate *(BANM, USAN, rINNM)*

Paliperidone, Palmitate de; Paliperidoni Palmitas; Palmitato de paliperidona; RO-92670; Палиперидона Палмитат.
(9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate.
$C_{39}H_{57}FN_4O_4$=664.9
CAS — 199739-10-1.
UNII — R8P8USM8FR.

Uses and Administration

Paliperidone is a benzisoxazole derivative and is the major active metabolite of the atypical antipsychotic risperidone (p. 1103.2). It is reported to be an antagonist at dopamine (D_2), serotonin (5-HT_2), adrenergic (α_1 and α_2), and histamine (H_1) receptors. It is used in the treatment of schizophrenia (p. 1031.3) and schizoaffective disorder. Paliperidone is given orally as the base and doses are expressed in terms of the base. It is also given intramuscularly as the long-acting palmitate ester; these doses are expressed in terms of either the ester or the base. Paliperidone palmitate 156 mg is equivalent to about 100 mg of paliperidone.

For the treatment of **schizophrenia**, the recommended oral dose of paliperidone is 6 mg once daily as a modified-release preparation; doses may range from 3 to 12 mg daily; dose increases should be made in steps of 3 mg at intervals of more than 5 days.

Intramuscular injection of paliperidone may be given into the deltoid or gluteal regions although the first 2 injections should be made into the deltoid muscle. Patients with no history of paliperidone or risperidone use should be given oral paliperidone or risperidone initially to assess tolerability. Intramuscular paliperidone may be given in an initial dose of 150 mg followed by 100 mg one week later. Thereafter, the recommended monthly maintenance dose is 75 mg with a range of 25 to 150 mg; further dose adjustments should be made at monthly intervals.

For the treatment of **schizoaffective disorder** as monotherapy or as an adjunct to mood stabilisers and/or antidepressants, paliperidone is given orally in doses similar to those used for schizophrenia except dose increases should be made at intervals of more than 4 days.

For details of dose reductions in patients with renal impairment, see below.

For details of uses and associated doses in children and adolescents, see Administration in Children, below.

References.
1. Dolder C, *et al.* Paliperidone for schizophrenia. *Am J Health-Syst Pharm* 2008; **65**: 403–13.
2. Nussbaum AM, Stroup TS. Paliperidone for the treatment of adults with schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 01/06/09).
3. Meltzer HY, *et al.* Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. *J Clin Psychiatry* 2008; **69**: 817–29.
4. Marino J, Caballero J. Paliperidone extended-release for the treatment of schizophrenia. *Pharmacotherapy* 2008; **28**: 1283–98.
5. Chwieduk CM, Keating GM. Paliperidone extended release: a review of its use in the management of schizophrenia. *Drugs* 2010; **70**: 1295–1317.
6. Owen RT. Paliperidone palmitate injection: its efficacy, safety and tolerability in schizophrenia. *Drugs Today* 2010; **46**: 463–71.
7. Canuso CM, *et al.* Role of paliperidone extended-release in treatment of schizoaffective disorder. *Neuropsychiatr Dis Treat* 2010; **6**: 667–79.
8. Gahr M, *et al.* Paliperidone extended-release: does it have a place in antipsychotic therapy? *Drug Des Devel Ther* 2011; **5**: 125–46.
9. Bossie CA, *et al.* Onset of efficacy and tolerability following the initiation dosing of long-acting paliperidone palmitate: post-hoc analyses of a randomized, double-blind clinical trial. *BMC Psychiatry* 2011; **11**: 79. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-11-79.pdf (accessed 13/10/11)
10. Yang LP. Oral paliperidone: a review of its use in the management of schizoaffective disorder. *CNS Drugs* 2011; **25**: 523–38.
11. Carter NJ. Extended-release intramuscular paliperidone palmitate: a review of its use in the treatment of schizophrenia. *Drugs* 2012; **72**: 1137–60.

Administration in children. In the USA, an oral modified-release preparation of paliperidone is licensed for the treatment of schizophrenia in adolescents aged 12 to 17 years. The recommended initial dose is 3 mg once daily; when necessary, dose increases should be made in steps of 3 mg at intervals of more than 5 days. Doses may range from 3 to 6 mg daily in those who weigh less than 51 kg or up to 12 mg daily in those weighing 51 kg or more.

References.
1. Singh J, *et al.* A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biol Psychiatry* 2011; **70**: 1179–87.

Administration in renal impairment. The plasma concentrations of paliperidone are increased in patients with renal impairment. The usual oral daily dosage (see above) should therefore be adjusted according to creatinine clearance (CC) as follows:
- CC 50 to 80 mL/minute: initially 3 mg once daily, may be increased thereafter to 6 mg once daily, according to response and tolerance
- CC 10 to 50 mL/minute: initially 1.5 mg once daily, may be increased thereafter to 3 mg once daily

Paliperidone, when given orally, has not been studied in patients with a CC of less than 10 mL/minute; use in such patients is not recommended.

The intramuscular dose should also be reduced as follows:
- CC 50 to 80 mL/minute: initially 100 mg followed, one week later, by 75 mg; thereafter, the recommended monthly maintenance dose is 50 mg with a range of 25 to 100 mg

Intramuscular use is not recommended in patients with a CC of less than 50 mL/minute.

Adverse Effects, Treatment, and Precautions

Although paliperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. The most frequent adverse effects with paliperidone are headache, dizziness, somnolence, sedation, agitation, fatigue, gastrointestinal effects such as constipation, dyspepsia, dry mouth, and nausea and vomiting, weight gain, extrapyramidal effects such as akathisia, dystonia, hypertonia, and tremor, tachycardia including sinus tachycardia, and nasopharyngitis. Other common adverse effects include blurred vision, orthostatic hypotension, arthralgia, back pain, and pain in the extremities. Tardive dyskinesia, small intestinal obstruction, and hyperprolactinaemia resulting in gynaecomastia, menstrual disturbances, amenorrhoea, and galactorrhoea occur rarely. Priapism has also been reported, as have neuroleptic malignant syndrome, agranulocytosis, leucopenia, and neutropenia.

Paliperidone has been associated with QT prolongation rarely and it should be used with caution in patients with cardiovascular disease, or with a family history of QT prolongation; certain drugs may also increase the risk (see Interactions, below).

Paliperidone should be used with caution in patients with renal or severe hepatic (Child-Pugh class C) impairment, with cardiovascular disease or other conditions predisposing to hypotension, with cerebrovascular disease, or with a history of seizures or conditions that lower the seizure threshold.

Paliperidone may affect the performance of skilled tasks such as driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics and recommendations for monitoring are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Formulation. As an oral modified-release preparation, paliperidone is contained within a non-absorbable tablet shell that releases the drug at a controlled rate. This biologically inert shell is eliminated intact in the faeces, along with other insoluble components of the tablet core.

Hypersensitivity. An anaphylactoid reaction to long-acting paliperidone palmitate injection has been reported[1] in a patient with established tolerance of oral risperidone; symptoms resolved with supportive treatment and oral risperidone was restarted without sequelae. An excipient, polyethylene glycol 4000, within the formulation was considered to be a possible causative agent.

1. Perry R, *et al.* Anaphylactoid reaction to paliperidone palmitate extended-release injectable suspension in a patient tolerant of oral risperidone. *Am J Health-Syst Pharm* 2012; **69**: 40–3.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by paliperidone. Additive effects may occur when paliperidone is given with drugs that can cause orthostatic hypotension. There may be an increased risk of QT prolongation when paliperidone is given with other drugs that are known to cause this effect. Paliperidone

may antagonise the actions of levodopa and other dopaminergics.

Paliperidone is a substrate of P-glycoprotein, and P-glycoprotein inducers such as carbamazepine may decrease paliperidone concentrations. The dose of paliperidone may need to be increased when given with such drugs and decreased when such drugs are stopped; full induction is achieved in 2 to 3 weeks and wears off over a similar period upon stopping the inducer.

Valproate may increase paliperidone concentrations and dose reduction of oral paliperidone may be required; however, this interaction is not expected to be clinically significant with intramuscular paliperidone.

Drugs that affect gastrointestinal transit time, such as metoclopramide, may affect the absorption of oral paliperidone.

Pharmacokinetics

Peak plasma-paliperidone concentrations occur about 24 hours after an oral dose and about 13 days after an intramuscular dose. Paliperidone is 74% bound to plasma proteins, mainly to α_1-acid glycoprotein and albumin. It is not extensively metabolised in the liver but undergoes dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. About 59% of a dose is excreted unchanged in the urine. The elimination half-life has been reported to be about 23 hours after oral dosage and ranging from 25 to 49 days after intramuscular dosage.

Paliperidone is distributed into breast milk.

References.
1. Boom S, *et al.* Single- and multiple-dose pharmacokinetics and dose proportionality of the psychotropic agent paliperidone extended release. *J Clin Pharmacol* 2009; 49: 1318–30.
2. Samtani MN, *et al.* Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. *Clin Pharmacokinet* 2009; 48: 585–600.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Invega; ***Austral.***: Invega; ***Austria***: Invega; ***Belg.***: Invega; Xeplion; ***Braz.***: Invega; ***Canad.***: Invega; ***China***: Invega (丙达); ***Cz.***: Invega; Xeplion; ***Denm.***: Invega; Xeplion; ***Fr.***: Invega†; Xeplion; ***Ger.***: Invega†; Xeplion; ***Gr.***: Invega; ***Hong Kong***: Invega; ***Hung.***: Invega; ***India***: Paliris; ***Indon.***: Invega; ***Irl.***: Invega; Xeplion; ***Israel***: Invega; Xeplion; ***Ital.***: Invega; ***Jpn***: Invega; ***Malaysia***: Invega; ***Mex.***: Inveda; ***Neth.***: Invega; Xeplion; ***Norw.***: Xeplion; ***NZ***: Invega; ***Philipp.***: Invega; ***Pol.***: Invega; ***Port.***: Invega; ***Rus.***: Invega (Инвега); ***Singapore***: Invega; ***Spain***: Invega; Xeplion; ***Swed.***: Invega; Xeplion; ***Switz.***: Invega; Xeplion; ***Thai.***: Invega; ***UK***: Invega; Xeplion; ***USA***: Invega.

Paraldehyde

Paracetaldehido; Paracetaldehyde; Paraldehid; Paraldehidas; Paraldehído; Paraldehit; Paraldehyd; Paraldéhyde; Paraldehydi; Paraldehydum; Паральдегид.

The trimer of acetaldehyde; 2,4,6-Trimethyl-1,3,5-trioxane.

$(C_2H_4O)_3$=132.2.

CAS — 123-63-7.

ATC — N05CC05.

ATC Vet — QN05CC05.

UNII — S6M3YBG8QA.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Paraldehyde). A colourless or slightly yellow, transparent liquid. It solidifies on cooling to form a crystalline mass. It may contain a suitable amount of an antoxidant. Relative density 0.991 to 0.996. F.p. is 10 degrees to 13 degrees; not more than 10% distils below 123 degrees and not less than 95% below 126 degrees. Soluble in water but less soluble in boiling water; miscible with alcohol and with volatile oils. Store in small well-filled airtight containers. Protect from light.

USP 36: (Paraldehyde). A colourless transparent liquid with a strong characteristic, but not unpleasant or pungent, odour. It is subject to oxidation to form acetic acid. It may contain a suitable stabiliser. Specific gravity is about 0.99. It has a congealing temperature of not lower than 11 degrees and distils completely between 120 degrees and 126 degrees. Soluble 1 in 10 of water v/v, but only 1 in 17 of boiling water v/v; miscible with alcohol, with chloroform, with ether, and with volatile oils. Store in well-filled airtight containers of not more than 30 mL at a temperature not exceeding 25 degrees. Protect from light. It must not be used more than 24 hours after opening the container.

Incompatibility. Paraldehyde exerts a solvent action upon rubber, polystyrene, and styrene-acrylonitrile copolymer and should not be given in plastic syringes made with these materials.

An evaluation of the compatibility of paraldehyde with plastic syringes and needle hubs concluded that, if possible, all-glass syringes should be used with paraldehyde.[1] Needles with plastic hubs could be used. Polypropylene syringes with rubber-tipped plastic plungers (*Plastipak*), or glass syringes with natural rubber-tipped plastic plungers (*Glaspak*) were acceptable only for the immediate administration or measurement of paraldehyde doses.

1. Johnson CE, Vigoreaux JA. Compatibility of paraldehyde with plastic syringes and needle hubs. *Am J Hosp Pharm* 1984; 41: 306–8.

Stability. Paraldehyde decomposes on storage, particularly after the container has been opened. Partly decomposed paraldehyde is **dangerous** if given. It must not be used if it has a brownish colour or a sharp penetrating odour of acetic acid.

Uses and Administration

Paraldehyde is a hypnotic and sedative with antiepileptic effects. However, because of the hazards associated with its use, its tendency to react with plastic, and the risks associated with its deterioration, it has largely been superseded by other drugs. It is still occasionally used to control status epilepticus (p. 510.2) resistant to conventional treatment. Given rectally or intramuscularly it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

At low temperature it solidifies to form a crystalline mass. If it solidifies, the whole should be liquefied before use.

A dose (expressed as undiluted paraldehyde) of 20 mL has been given rectally. Paraldehyde should be diluted before it is given; prediluted enemas of 8 to 50% are available in some countries, such as the UK.

The usual intramuscular dose is 5 to 10 mL. Doses should be given by deep injection into the buttocks and not more than 5 mL should be administered at each injection site.

For doses in children, see below.

Paraldehyde has been given by slow intravenous infusion in specialist centres with intensive care facilities but this route is not usually recommended; it must be diluted in sodium chloride 0.9% before use.

Paraldehyde has been given orally; it should always be well diluted to avoid gastric irritation.

References.
1. Rowland AG, *et al.* Review of the efficacy of rectal paraldehyde in the management of acute and prolonged tonic-clonic convulsions. *Arch Dis Child* 2009; 94: 720–3.

Administration in children. Paraldehyde may be used in children to control status epilepticus resistant to conventional treatment. Although unlicensed, the *BNFC* suggests that a single rectal dose (expressed as undiluted paraldehyde) of 0.4 mL/kg (maximum of 10 mL) may be given to neonates and children up to 18 years of age. Paraldehyde should be diluted before use. In some countries, it is also licensed for use by deep intramuscular injection; a dose of 0.1 to 0.15 mL/kg may be given every 4 to 8 hours. No more than 5 mL should be administered at each injection site.

Dependence and Withdrawal

Prolonged use of paraldehyde may lead to dependence, especially in alcoholics. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects and Treatment

Paraldehyde decomposes on storage and deaths from corrosive poisoning have followed the use of such material. Paraldehyde has an unpleasant taste and imparts a smell to the breath; it may cause skin rashes.

Oral or rectal use of paraldehyde may cause gastric or rectal irritation. Intramuscular injection is painful and associated with tissue necrosis, sterile abscesses, and nerve damage. Intravenous use is extremely hazardous since it may cause pulmonary oedema and haemorrhage, hypotension and cardiac dilatation, and circulatory collapse; thrombophlebitis is also associated with intravenous use.

Overdosage results in rapid laboured breathing owing to damage to the lungs and to acidosis. Nausea and vomiting may follow oral overdoses. Respiratory depression and coma as well as hepatic and renal damage may occur. Treatment is as for barbiturate overdose (see Amobarbital, p. 1038.1).

Precautions

Paraldehyde should not be given to patients with gastric disorders and it should be used with caution, if at all, in patients with bronchopulmonary disease or hepatic impairment. It should not be given rectally in the presence of colitis. Old paraldehyde must never be used.

Paraldehyde must be well diluted before oral or rectal use; if it is deemed essential to give paraldehyde intravenously it must be well diluted and given very slowly with extreme caution (see also Adverse Effects, above and Uses, above). Intramuscular injections may be given undiluted but care should be taken to avoid nerve damage. Plastic syringes should be avoided (see Incompatibility, above).

Interactions

The sedative effects of paraldehyde are enhanced by CNS depressants such as alcohol, barbiturates, and other sedatives. A few case reports suggest that disulfiram may enhance the toxicity of paraldehyde; use together is not recommended.

Pharmacokinetics

Paraldehyde is generally absorbed readily, although absorption is reported to be slower after rectal than after oral or intramuscular doses. It is widely distributed and has a reported half-life of 4 to 10 hours. About 80% of a dose is metabolised in the liver probably to acetaldehyde, which is oxidised by aldehyde dehydrogenase to acetic acid. Unmetabolised drug is largely excreted unchanged through the lungs; only small amounts appear in the urine. It crosses the placental barrier and is distributed into breast milk.

Preparations

Pharmacopoeial Preparations

BP 2014: Paraldehyde Injection.

Penfluridol *(BAN, USAN, rINN)*

McN-JR-16341; Penfluridoli; Penfluridolum; R-16341; Пенфлуридол.

4-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(*p,p'*-difluorobenzhydryl)propyl]piperidin-4-ol.

$C_{28}H_{27}ClF_5NO$=524.0

CAS — 26864-56-2.

ATC — N05AG03.

ATC Vet — QN05AG03.

UNII — 25TLU22O8H.

Pharmacopoeias. In *Chin.*

Profile

Penfluridol is a diphenylbutylpiperidine antipsychotic and shares the general properties of the phenothiazine, chlorpromazine (p. 1045.2). After oral doses it has a prolonged duration of action that lasts for about a week. It is used in the treatment of psychoses including schizophrenia (below).

The usual oral dose of penfluridol for the treatment of chronic psychoses is 20 to 60 mg once a week. Doses of up to 250 mg once a week may be required in severe or resistant conditions.

Schizophrenia. A systematic review[1] concluded that penfluridol appears to have a similar efficacy and adverse effects profile to other classical antipsychotics used in the treatment of schizophrenia (p. 1031.3). The authors also suggested that penfluridol, in a weekly oral dose of 40 to 80 mg, is a suitable alternative, particularly for patients who do not respond to daily oral medication or adapt well to depot drugs.

1. Soares BGO, Lima MS. Penfluridol for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/03/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Semap; ***Braz.***: Semap; ***Denm.***: Semap†; ***Gr.***: Flupidol; Semap; ***India***: Flump; ***Israel***: Semap†; ***Mex.***: Semap; ***Neth.***: Semap; ***Switz.***: Semap†.

Pentobarbital *(BAN, rINN)*

Aethaminalum; Mebubarbital; Mebumal; Pentobarbitaali; Pentobarbital; Pentobarbitalis; Pentobarbitalum; Pentobarbitone; Пентобарбитал.

5-Ethyl-5-(1-methylbutyl)barbituric acid.

$C_{11}H_{18}N_2O_3$=226.3

CAS — 76-74-4.

ATC — N05CA01.

ATC Vet — QN05CA01; QN51AA01.

UNII — I4744080IR.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of pentobarbital:

Blockbuster; Menish; Nebbies; Nembies; Nemish; Nemmies; Nimbies; Nimby; Yellow; Yellow bullets; Yellow dolls; Yellow jackets; Yellow submarines; Yellows.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pentobarbital). Colourless crystals or a white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 36: (Pentobarbital). A white or practically white, practically odourless, fine powder. Very slightly soluble in water and in carbon tetrachloride; soluble 1 in 4.5 of alcohol, 1 in 4 of chloroform, and 1 in 10 of ether; very soluble in acetone and in methyl alcohol; soluble in benzene. Store in airtight containers.

Pentobarbital Calcium *(BANM, rINNM)*

Calcii Pentobarbitalum; Pentobarbital cálcico; Pentobarbital Calcique; Pentobarbitone Calcium; Кальций Пентобарбитал.

Calcium 5-ethyl-5-(1-methylbutyl)barbiturate.

$(C_{11}H_{17}N_2O_3)_2Ca$=490.6

ATC — N05CA01.

ATC Vet — QN05CA01.

Pharmacopoeias. In *Jpn.*

Pentobarbital Sodium *(BANM, rINNM)*

Aethaminalum-Natrium; Ethaminal Sodium; Mebumalnatrium; Natrii Pentobarbitalum; Pentobarbitaalinatrium; Pentobarbital-Natrium; Pentobarbital sódico; Pentobarbital Sodique; Pentobarbital sodná sůl; Pentobarbitalio natrio druska; Pentobarbitalnatrium; Pentobarbitál-nátrium; Pentobarbitalum natricum; Pentobarbitone Sodium; Sodium Pentobarbital; Soluble Pentobarbitone; Натрий Пентобарбитал.

Sodium 5-ethyl-5-(1-methylbutyl)barbiturate.

$C_{11}H_{17}N_2NaO_3$=248.3

CAS — 57-33-0.

ATC — N05CA01.

ATC Vet — QN05CA01.

UNII — NJJ0475N0S.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pentobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Very soluble in water. A 10% solution in water has a pH of 9.6 to 11.0 when freshly prepared. Store in airtight containers.

USP 36: (Pentobarbital Sodium). White, crystalline granules or white powder. Is odourless or has a slight characteristic odour. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. pH of a 10% solution in water is between 9.8 and 11.0. Solutions decompose on standing, the decomposition being accelerated at higher temperatures. Store in airtight containers.

Incompatibility. Pentobarbital may be precipitated from preparations containing pentobarbital sodium, depending on the concentration and pH. Pentobarbital sodium has, therefore, been reported to be incompatible with many other drugs particularly acids and acidic salts.

Uses and Administration

Pentobarbital is a barbiturate that has been used as a hypnotic and sedative. It has general properties and uses similar to those of amobarbital (p. 1037.3). It has been used as a sedative and in the short-term management of insomnia (p. 1033.2) but barbiturates are not considered appropriate for such purposes. Pentobarbital sodium has also been used for premedication in anaesthetic procedures (p. 1899.1), but barbiturates for pre-operative sedation have been replaced by other drugs. It has been given parenterally as part of the emergency management of acute seizures including status epilepticus (p. 510.2) although the short-acting barbiturate thiopental is usually used. Pentobarbital is usually given as the sodium salt, although pentobarbital itself and its calcium salt have both been used.

A usual oral dose of pentobarbital sodium for insomnia was 100 to 200 mg, given at bedtime. Usual parenteral doses for other indications were 150 to 200 mg as a single intramuscular dose or 100 mg by slow intravenous injection.

Cerebrovascular disorders. Barbiturate-induced coma (commonly with pentobarbital or thiopental) has been used, both therapeutically and prophylactically, to protect the brain from ischaemia (see under Thiopental, p. 1919.1), and for raised intracranial pressure (p. 1271.3) refractory to conventional therapies, although there has been debate as to efficacy and safety.

References.
1. Marshall GT, *et al.* Pentobarbital coma for refractory intra-cranial hypertension after severe traumatic brain injury: mortality predictions and one-year outcomes in 55 patients. *J Trauma* 2010; 69: 275–83.

Dependence and Withdrawal

As for Amobarbital, p. 1038.1.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p. 1038.1.

Formulation. For a report of lactic acidosis associated with intravenous infusion of a parenteral formulation of pentobarbital containing propylene glycol, see Toxicity under Propylene Glycol, p. 2205.3.

Interactions

As for Amobarbital, p. 1038.2.

Pharmacokinetics

Pentobarbital is well absorbed from the gastrointestinal tract after oral or rectal doses, and is reported to be about 60 to 70% bound to plasma proteins. The elimination half-life appears to be dose-dependent and reported values have ranged from 15 to 50 hours. Pentobarbital is metabolised in the liver, mainly by hydroxylation, and excreted in the urine mainly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Mebumal; ***Jpn***: Ravona; ***S.Afr.***: Sopental†; ***USA***: Nembutal.

Multi-ingredient Preparations. ***Arg.***: Dimaval; ***USA***: Cafatine-PB.

Pharmacopoeial Preparations
BP 2014: Pentobarbital Tablets;
USP 36: Pentobarbital Sodium Injection.

Perazine Dimalonate

P-725 (perazine); Pemazine Dimalonate; Perazina, dimalonato de.

10-[3-(4-Methylpiperazin-1-yl)propyl]phenothiazine dimalonate.

$C_{20}H_{25}N_3S,2C_3H_4O_4$=547.6

CAS — 84-97-9 (perazine); 14777-25-4 (perazine dimalonate).

ATC — N05AB10.

ATC Vet — QN05AB10.

Pharmacopoeias. *Pol.* includes only an injection of the dimalonate. It also includes a monograph for Perazine Dimaleate.

Profile

Perazine dimalonate is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2) and is used for the treatment of psychotic conditions. It has a piperazine side-chain. It is given orally as the dimalonate although doses are expressed in terms of the base; perazine dimalonate 40.3 mg is equivalent to about 25 mg of perazine. Usual doses are the equivalent of 50 to 600 mg of the base daily; up to 1 g daily has been given in resistant cases. It has also been given intramuscularly.

Perazine dimaleate given orally has been used similarly.

Adverse effects. Acute axonal neuropathies of superficial nerve fibres developed in 5 patients receiving perazine dimalonate after exposure to sunlight.[1]

1. Roelcke U, *et al.* Acute neuropathy in perazine-treated patients after sun exposure. *Lancet* 1992; 340: 729–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Taxilan; ***Pol.***: Peragal; Perazin; Perazyna†; Pernazinum.

Pericyazine *(BAN)*

Periciazin; Periciazina; Periciazine (pINN); Péricyazine; Periciazinum; Perislatsiini; Propericiazine; RP-8909; SKF-20716; Перициазин.

10-[3-(4-Hydroxypiperidino)propyl]phenothiazine-2-carbonitrile; 1-[3-(2-Cyanophenothiazin-10-yl)propyl]piperidin-4-ol.

$C_{21}H_{23}N_3OS$=365.5

CAS — 2622-26-6.

ATC — N05AC01.

ATC Vet — QN05AC01.

UNII — 3405M6FD73.

Uses and Administration

Pericyazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain. It is used in the treatment of psychoses including schizophrenia (p. 1031.3) and disturbed behaviour (p. 1030.2), and in the short-term management of severe anxiety (p. 1028.1).

Pericyazine is usually given as the base but the mesilate and tartrate have also been used.

The usual oral dose for the treatment of severe anxiety, agitation, aggression, or impulsive behaviour is 15 to 30 mg daily given in 2 divided doses, the larger amount in the evening. In schizophrenia and severe psychoses initial doses of 75 mg daily may be given in divided doses, increased if necessary, at weekly intervals by increments of 25 mg, to a maximum of 300 mg daily.

Elderly patients should be given reduced doses: a recommended initial dose is 5 to 10 mg daily for anxiety or disturbed behaviour and 15 to 30 mg daily for schizophrenia or psychosis, both in divided doses.

For details of doses in children, see below.

Administration in children. For the treatment of behavioural disorders and schizophrenia in children, a recommended initial oral dose of pericyazine in those aged 1 year and over is 500 micrograms daily for a child weighing 10 kg; for heavier children this initial dose may be increased by 1 mg for each additional 5 kg, to a maximum total of 10 mg daily. Doses may be gradually increased according to response but the daily maintenance dose should not exceed twice the initial dose. Children aged 12 years and over may be given the usual adult dose (see above).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Sedation and orthostatic hypotension may be marked.

Interactions

As for Chlorpromazine, p. 1051.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Neuleptil; ***Austral.***: Neulactil; ***Braz.***: Neuleptil; ***Canad.***: Neuleptil; ***Chile***: Neuleptil; ***Denm.***: Neulactil; ***Fin.***: Neulactil; ***Fr.***: Neuleptil; ***Gr.***: Nemactil; Neuleptil; ***Hong Kong***: Neulactil; ***Israel***: Neuleptil; ***Ital.***: Neuleptil; ***Neth.***: Neuleptil; ***NZ***: Neulactil; ***Rus.***: Neuleptil (Неулептил); ***Spain***: Nemactil; ***UK***: Neulactil; ***Venez.***: Neuleptil.

Perospirone Hydrochloride *(rINNM)*

Hidrocloruro de perospirona; Perospirona, hidrocloruro de; Pérospirone, Chlorhydrate de; Perospironi Hydrochloridum; SM-9018; Перospирона Гидрохлорид.

cis-N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-cyclohexanedicarboximide hydrochloride.

$C_{23}H_{30}N_4O_2S$,HCl=463.0

CAS — 150915-41-6 (perospirone); 129273-38-7 (perospirone hydrochloride).

UNII — T884I76TMN (perospirone hydrochloride); S03S4466IP (perospirone hydrochloride dihydrate).

Profile

Perospirone is an antipsychotic used in the treatment of schizophrenia (p. 1031.3). Although it has been described as an atypical antipsychotic, the incidence of extrapyramidal effects may be rather higher than is usually seen with atypical drugs such as clozapine (p. 1057.3). Perospirone hydrochloride is given in usual oral doses of 12 to 48 mg daily in 3 divided doses.

References.
1. Onrust SV, McClellan K. Perospirone. *CNS Drugs.* 2001; 15: 329–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kang Er Ting (康尔汀); ***Jpn***: Lullan.

Perphenazine *(BAN, rINN)*

Perfenatsiini; Perfenazin; Perfenazina; Perfenazinas; Perfenazyna; Perphenazin; Perphénazine; Perphenazinum; Перфеназин.

2-[4-[3-(2-Chlorophenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

$C_{21}H_{26}ClN_3OS$=404.0

CAS — 58-39-9.

ATC — N05AB03.

ATC Vet — QN05AB03.
UNII — FTA7XXY4EZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Jpn also includes the maleate.

Ph. Eur. 8: (Perphenazine). A white or yellowish-white crystalline powder. M.p. 96 degrees to 100 degrees. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute solutions of hydrochloric acid. Protect from light.

USP 36: (Perphenazine). A white to creamy-white odourless powder. M.p. 94 degrees to 100 degrees. Practically insoluble in water; soluble 1 in 7 of alcohol and 1 in 13 of acetone; freely soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Perphenazine has been reported to be incompatible with cefoperazone sodium[1] and with midazolam hydrochloride (see p. 1085.1).

1. Gasca M, *et al.* Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.

Perphenazine Decanoate *(BANM, rINNM)*

Decanoato de perfenazina; Perfenazina, decanoato de; Perphénazine, Décanoate de; Perphenazini Decanoas; Перфеназина деканоат.

$C_{31}H_{44}ClN_3O_2S$=558.2
ATC — N05AB03.
ATC Vet — QN05AB03.

Perphenazine Enantate *(BANM, rINNM)*

Enantato de perfenazina; Perfenazina, enantato de; Perphénazine, Enantate de; Perphenazine Enanthate; Perphenazine Heptanoate; Perphenazini Enantas; Перфеназина энантат.

$C_{28}H_{38}ClN_3O_2S$=516.1
CAS — 17528-28-8.
ATC — N05AB03.
ATC Vet — QN05AB03.
UNII — Z6RS3DKN8J.

Uses and Administration

Perphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain. It is used in the treatment of various psychoses including schizophrenia (p. 1031.3) and mania (see Bipolar Disorder, p. 397.2) as well as disturbed behaviour (p. 1030.2) and in the short-term, adjunctive management of severe anxiety (p. 1028.1). Perphenazine is also used for the management of postoperative or chemotherapy-induced nausea and vomiting (p. 1814.3) and for the treatment of intractable hiccup (p. 1046.3).

Perphenazine is usually given orally as the base; it has also been given by intramuscular or intravenous injection. The fendizoate derivative has also been given orally. Long-acting decanoate or enantate esters of perphenazine, given by intramuscular injection, are available in some countries.

The usual initial oral dose for the treatment of **schizophrenia, mania, and other psychoses** is 4 mg three times daily. The dose is adjusted according to response up to a usual maximum of 24 mg daily, although up to 64 mg daily has occasionally been used in hospitalised patients. Similar doses have been used for the management of **severe agitated or violent behaviour** or in **severe anxiety**. Perphenazine has sometimes been used in preparations with tricyclic antidepressants such as amitriptyline in the treatment of anxiety with depression.

For the **control of nausea and vomiting** the usual oral dose is 4 mg three times daily but up to 8 mg three times daily may be required.

The long-acting decanoate or enantate esters of perphenazine are given by deep intramuscular injection in doses ranging from about 50 to 300 mg of ester given at intervals of 2 to 4 weeks.

Perphenazine and its esters should be given in reduced doses to the elderly but it should be noted that they are not indicated for the management of agitation and restlessness in these patients.

References.

1. Hartung B, *et al.* Perphenazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 14/04/05).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Perphenazine has been associated with a lower frequency of sedation, but a higher incidence of extrapyramidal effects.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of perphenazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The distribution of perphenazine into breast milk was studied[2] in a mother who was receiving oral perphenazine 24 mg daily, later reduced to 16 mg daily. Breast feeding was started after it was estimated that a breast-fed infant would ingest about 0.1% of a maternal dose. Treatment with perphenazine lasted for 3.5 months and during this period the child thrived normally and no drug-induced symptoms were seen.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Olesen OV, *et al.* Perphenazine in breast milk and serum. *Am J Psychiatry* 1990; **147:** 1378–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies perphenazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Perphenazine is well absorbed after oral doses and undergoes some first-pass metabolism, resulting in a relative bioavailability of about 60 to 80%. Peak plasma concentrations occur between 1 to 3 hours after ingestion. It is widely distributed and crosses the placenta. Perphenazine is extensively metabolised; up to 70% is excreted in the urine mainly as metabolites, with about 5% being excreted in the faeces. The plasma elimination half-life of perphenazine is between 9 and 12 hours. Perphenazine decanoate and perphenazine enantate are slowly absorbed from the site of intramuscular injection. They gradually release perphenazine into the body and are therefore suitable for use as depot injections.

Perphenazine 5 or 6 mg given intravenously had a plasma half-life from 8.4 to 12.3 hours in a study of 4 schizophrenic patients and 4 healthy subjects.[1] Plasma-perphenazine concentrations varied considerably 3 to 5 hours after dosing; this was followed by an exponential elimination phase. Plasma concentrations were undetectable after a 6-mg oral dose in 4 healthy subjects and only low plasma concentrations of its sulfoxide metabolite could be detected; this was attributed to a marked first-pass effect. Systemic availability was also variable and poor in 4 schizophrenic patients given perphenazine 12 mg three times daily. However, it was considered that oral therapy should be given at 8-hour intervals. Intramuscular injection of perphenazine enantate 50 or 100 mg every 2 weeks gave plasma-perphenazine concentrations similar to those after continuous oral dosage, but high initial absorption in the first 2 to 3 days was associated with serious CNS adverse effects.

1. Hansen CE, *et al.* Clinical pharmacokinetic studies of perphenazine. *Br J Clin Pharmacol* 1976; **3:** 915–23.

Metabolism. In 12 healthy subjects there was a clear difference in the disposition of a single oral dose of perphenazine between poor and extensive hydroxylators of debrisoquine.[1]

1. Dahl-Puustinen M-L, *et al.* Disposition of perphenazine is related to polymorphic debrisoquin hydroxylation in human beings. *Clin Pharmacol Ther* 1989; **46:** 78–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Decentan†; ***Denm.***: Trilafon; ***Fin.***: Peratsin; ***Fr.***: Trilifan†; ***Ger.***: Decentan; ***Hong Kong***: Synazin†; ***Indon.***: Trilafon; ***Irl.***: Fentazin; ***Israel***: Perphenan; ***Ital.***: Trilafon; ***Jpn***: PZC; ***Mex.***: Leptopsique; ***Norw.***: Trilafon; ***Philipp.***: Trilafon†; ***Pol.***: Trilafon; ***Rus.***: Etaperazin (Этаперазин); ***Spain***: Decentan; ***Swed.***: Trilafon; ***Switz.***: Trilafon; ***Thai.***: Conazine; Pernamed; Pernazine; Perzine; Porazine; ***UK***: Fentazin.

Multi-ingredient Preparations. ***Arg.***: Karile; ***Canad.***: Apo-Peram†; PMS-Levazine; ***Fin.***: Pertripty!; ***Gr.***: Minitran; Triphenaze; ***Indon.***: Mutabon-D; Mutabon-M; ***Ital.***: Mutabon; ***Mex.***: Adepsique; ***Port.***: Mutabon; ***Spain***: Mutabase; ***Thai.***: Neuragon†; Polybon; ***UK***: Triptafen; ***USA***: Etrafon†.

Pharmacopoeial Preparations
BP 2014: Perphenazine Tablets;
USP 36: Perphenazine and Amitriptyline Hydrochloride Tablets; Perphenazine Injection; Perphenazine Oral Solution; Perphenazine Syrup; Perphenazine Tablets.

Phenazepam

Fenazepam; Феназепам.
7-Bromo-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.
$C_{15}H_{10}BrClN_2O$=349.6
CAS — 51753-57-2.
UNII — 3DSB43090Z.

Profile

Phenazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is used in the short-term treatment of anxiety disorders and as an anticonvulsant. There have been concerns about abuse (see Overdosage, below).

Overdosage. Severe intoxication resulting from abuse of a 400- to 600-mg dose of phenazepam (usual single dose up to 1 mg) has been reported in a patient in Sweden. The authors reported that the half-life of phenazepam was about 60 hours and in other cases patients had still shown symptoms more than 14 days after ingestion.[1]

Abuse of phenazepam has been reported in several other countries, including Finland, the UK, and the USA; screening of post-mortem blood samples in Scotland between January and July 2011 identified 9 deaths where phenazepam was present, in all cases in persons with a history of drug misuse.[2]

1. Mrozkowska J, *et al.* Missbruk av fenazepam—ny företeelse i Sverige. Bensodiazepinderivat från Ryssland gav svår intoxikation. *Lakartidningen* 2009; **106:** 516–17.
2. Maskell PD, *et al.* Phenazepam is currently being misused in the UK. *BMJ* 2011; **343:** 59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Elzepam (Элзепам); Phenorelaxan (Фенорелаксан); Phezipam (Фезипам); Trankvezipam (Транквезипам).

Phenprobamate *(BAN, rINN)*

Fenprobamaatti; Fenprobamat; Fenprobamato; MH-532; Phenprobamatum; Proformiphen; Фенпробамат.
3-Phenylpropyl carbamate.
$C_{10}H_{13}NO_2$=179.2
CAS — 673-31-4.
ATC — M03BA01.
ATC Vet — QM03BA01.
UNII — UJZ473TPS0.

Profile

Phenprobamate is a carbamate with general properties similar to those of meprobamate (p. 1083.3). It has been used for its anxiolytic and muscle relaxant actions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Gamaflex; Gamakuil.

Multi-ingredient Preparations. ***Turk.***: Kuiflex; Kuilil.

Pimozide *(BAN, USAN, rINN)*

McN-JR-6238; Pimotsidi; Pimozid; Pimozida; Pimozidas; Pimozidum; Pimozyd; R-6238; Пимозид.
1-{1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidyl}benzimidazolin-2-one; 1-{1-[3-(4,4'-Difluorobenzhydryl)propyl]-4-piperidyl}benzimidazolin-2-one.
$C_{28}H_{29}F_2N_3O$=461.6
CAS — 2062-78-4.
ATC — N05AG02.
ATC Vet — QN05AG02.
UNII — 1HIZ4DL86F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Pimozide). A white or almost white powder Practically insoluble in water; slightly soluble in alcohol soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Pimozide). A white crystalline powder. Insoluble in water; soluble 1 in 1000 of alcohol, of ether, and of methyl alcohol, 1 in 100 of acetone, 1 in 10 of chloroform and 1 in more than 1000 of 0.1N hydrochloric acid. Store in airtight containers. Protect from light.

Uses and Administration

Pimozide is a diphenylbutylpiperidine antipsychotic and is structurally similar to the butyrophenones. It is a long

acting antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3), although it also has some calcium-blocking activity. Pimozide is given orally in the management of psychoses including schizophrenia (below), paranoid states, and monosymptomatic hypochondria (p. 1030.2) and in Tourette's syndrome (below). An ECG should be performed in all patients before starting treatment with pimozide (see Adverse Effects, Treatment, and Precautions, below).

In **schizophrenia**, treatment is usually begun with a dose of 2 mg daily (the *BNFC* suggests 1 mg in those aged 12 to 18 years), adjusted thereafter according to response in increments of 2 to 4 mg at intervals of not less than 1 week. The usual dose range is 2 to 20 mg daily. It is generally given as a single daily dose.

In **monosymptomatic hypochondria and paranoid psychoses**, the initial dose is 4 mg daily adjusted as above to a maximum daily dose of 16 mg.

Pimozide treatment should start at half the usual initial dosage in elderly patients.

In the USA, pimozide is only licensed for the treatment of **Tourette's syndrome**; initial doses are 1 to 2 mg daily in divided doses, increased thereafter every other day to a maximum of 10 mg daily or 200 micrograms/kg daily. Dose adjustment has been suggested for patients who are poor CYP2D6 metabolisers; see Administration in Genetic Variation, below. For details of doses in children, see below.

Administration in children. In the USA, pimozide is licensed for the treatment of children with Tourette's syndrome; initial oral doses are 50 micrograms/kg once daily at bedtime, increased thereafter every third day to a maximum of 200 micrograms/kg (not exceeding 10 mg) daily. US licensed product information also suggests that genotyping for cytochrome P450 isoenzyme CYP2D6 should be performed when the dose is increased above 50 micrograms/kg daily, that this is the maximum recommended dose in CYP2D6 poor metabolisers, and that the interval between dose increases should be at least 14 days in these patients.

Although not licensed in the UK, the *BNFC* suggests that children aged 2 to 12 years may be given oral doses of 1 to 4 mg daily and those aged 12 to 18 years, 2 to 10 mg daily.

For doses in adolescents with schizophrenia, see Uses and Administration, p. 1096.3.

Administration in genetic variation. US licensed product information for pimozide suggests that genotyping for cytochrome P450 isoenzyme CYP2D6 should be performed when the oral dose is increased above 4 mg daily, that this is the maximum recommended dose in CYP2D6 poor metabolisers, and that the interval between dose increases should be at least 14 days in these patients. (In the USA, pimozide is only licensed for the treatment of Tourette's syndrome.)

For dosage adjustment in children, see above.

Chorea. Antipsychotics such as pimozide have some action against choreiform movements (p. 1029.3) as well as being of use to control the behavioural disturbances of Huntington's chorea.

References.

1. Shannon KM, Fenichel GM. Pimozide treatment of Sydenham's chorea. *Neurology* 1990; 40: 186.

Dystonia. *Antipsychotics* such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to other drugs.[1] In very severe dystonia combination therapy may be required. Pimozide in gradually increasing doses up to 12 mg daily with tetrabenazine and trihexyphenidyl is sometimes effective. However, antipsychotics often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p. 1049.2).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; 300: 139–44.

Schizophrenia. A systematic review[1] concluded that pimozide appears to be of similar efficacy to other classical antipsychotics in the treatment of schizophrenia (p. 1031.3). There was no evidence that it was particularly useful for those with delusional disorders or with mainly negative symptoms.

1. Rathbone J, McMonagle T. Pimozide for schizophrenia or related psychoses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 20/03/08).

Taste disorders. For reference to the use of pimozide in the treatment of taste disorders, see under Chlorpromazine, p. 1047.2.

Tourette's syndrome. Tourette's syndrome (see Tics, p. 1030.1) is a disorder characterised by motor and vocal tics and behavioural disturbances. Many patients with Tourette's syndrome do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide[1-3] have been most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. Pimozide may be slightly less effective than haloperidol, but adverse effects are also less frequent.[3] Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al.* Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; 46: 722–30.
2. Sallee FR, *et al.* Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; 154: 1057–62.
3. Pringsheim T, Marras C. Pimozide for tics in Tourette's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 28/09/09).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Extrapyramidal effects may be more common than with chlorpromazine but pimozide may be less likely to cause sedation, hypotension, or antimuscarinic effects.

Ventricular arrhythmias and other ECG abnormalities, such as prolongation of the QT interval and T-wave changes, have been associated with the use of pimozide; an ECG should therefore be performed before, and repeated periodically during, treatment. If repolarisation changes appear or arrhythmias develop, the need for continuing treatment should be reviewed; the dose of pimozide should be reduced or, if the QT interval exceeds 500 milliseconds, therapy should be withdrawn. Pimozide is contra-indicated in patients with pre-existing prolongation of the QT interval, or a family history of congenital QT prolongation, and in patients with a history of cardiac arrhythmias. Electrolyte disturbances such as hypokalaemia or hypomagnesaemia in patients receiving pimozide may lead to cardiotoxicity.

Effects on the cardiovascular system. The UK CSM has received reports of ventricular arrhythmias and other ECG abnormalities such as prolongation of the QT interval and T-wave changes associated with the use of pimozide.[1,2] In August 1990 they had received 13 reports of sudden unexpected death since 1971; many of these patients had no evidence of pre-existing cardiac disease, and 7 were under 30 years of age. Five of the 13 were also taking other antipsychotics. Most cases were associated with doses greater than 20 mg daily and many had had the dose increased rapidly, possibly resulting in substantial tissue accumulation. By February 1995 the CSM had received a total of 40 reports (16 fatal) of serious cardiac reactions most of which involved arrhythmias.

See also under Chlorpromazine, p. 1047.3.

1. CSM. Cardiotoxic effects of pimozide. *Current Problems 29* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024447&RevisionSelectionMethod=LatestReleased (accessed 07/08/08)
2. CSM/MCA. Cardiac arrhythmias with pimozide (Orap). *Current Problems* 1995; 21: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Genetic factors. The metabolism of pimozide is mediated to some extent by the cytochrome P450 isoenzyme CYP2D6. Patients who are poor CYP2D6 metabolisers may have higher concentrations of pimozide than those who are extensive metabolisers, and their dosage of pimozide may need to be amended; for further details, see Administration in Genetic Variation, above.

Interactions

As for Chlorpromazine, p. 1051.3. The risk of arrhythmias with pimozide may be increased by other drugs that prolong the QT interval including some antiarrhythmics, other antipsychotics (including depot preparations), tricyclic antidepressants, the antihistamines terfenadine and astemizole, antimalarials, and cisapride; use together should be avoided. Use with drugs that induce electrolyte disturbances, such as diuretics, should also be avoided.

The use of pimozide with drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 is contra-indicated; the resultant decrease in the metabolism of pimozide may lead to increased plasma concentrations and hence greater risk of cardiac arrhythmias. CYP3A4 inhibitors include the macrolide antibacterials such as clarithromycin, erythromycin, and troleandomycin; the azole antifungals including itraconazole and ketoconazole; the HIV-protease inhibitors; the NNRTIs; nefazodone, and zileuton. The metabolism of pimozide may also be inhibited by grapefruit juice and use together should be avoided.

Pimozide is also metabolised by CYP2D6, albeit to a lesser extent, and *in vitro* data indicate that the CYP2D6 inhibitor quinidine may reduce the metabolism of pimozide; UK licensed product information contra-indicates the use of such inhibitors with pimozide. The isoenzyme CYP1A2 may also be involved in the metabolism of pimozide and consequently there is a theoretical possibility of interactions with CYP1A2 inhibitors.

Pimozide should also not be used with SSRIs such as citalopram, escitalopram, paroxetine, and sertraline. Paroxetine and sertraline have been reported to increase the plasma concentrations of pimozide, and hence there may be a greater risk of QT prolongation. Citalopram and escitalopram have been reported to prolong the QT interval when used with pimozide; the mechanism of this interaction is unknown. Use of pimozide with SSRIs has also been reported to cause extrapyramidal effects, oculogyric crises, and sedation.

Antibacterials. Sudden deaths have occurred in patients given pimozide and *clarithromycin*, see p. 1052.1.

Pharmacokinetics

More than half of an oral dose of pimozide is reported to be absorbed. It undergoes significant first-pass metabolism. Peak plasma concentrations have been reported after 4 to 12 hours and there is a considerable interindividual variation in the concentrations achieved. Pimozide is metabolised in the liver mainly by *N*-dealkylation and excreted in the urine and faeces in the form of metabolites and unchanged drug. Metabolism is mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP2D6; CYP1A2 may also be involved. Pimozide has a mean elimination half-life of about 55 hours, although half-lives of up to 150 hours have been noted in some patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Orap; *Austral.*: Orap†; *Austria*: Orap; *Belg.*: Orap; *Braz.*: Orap; *Canad.*: Orap; *Chile*: Orap; *Denm.*: Orap; *Fr.*: Orap; *Ger.*: Orap; *Gr.*: Pirium; *Hong Kong*: Orap; *India*: Larap; Neurap; Orap; *Indon.*: Orap; *Irl.*: Orap; *Israel*: Orap; *Ital.*: Orap; *Jpn*: Orap; *Neth.*: Orap; *NZ*: Orap†; *Port.*: Orap; *S.Afr.*: Orap; *Singapore*: Orap; *Spain*: Orap; *Thai.*: Orap†; Pizide; *Turk.*: Norofren; *UK*: Orap; *USA*: Orap; *Venez.*: Orap.

Pharmacopoeial Preparations
BP 2014: Pimozide Tablets;
USP 36: Pimozide Tablets.

Pinazepam *(rINN)*

Pinazépam; Pinazepamum; Пиназепам.
7-Chloro-1,3-dihydro-5-phenyl-1-(prop-2-ynyl)-2*H*-1,4-benzodiazepin-2-one.
$C_{18}H_{13}ClN_2O$=308.8
CAS — 52463-83-9.
ATC — N05BA14.
ATC Ver — QN05BA14.
UNII — 5286R8Z882.

Profile

Pinazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is given in usual oral doses of 5 to 20 mg daily in divided doses for the short-term treatment of anxiety disorders (p. 1028.1). Doses of 2.5 to 5 mg at night have been used in the treatment of insomnia (p. 1033.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hong Kong*: Domar; *Ital.*: Domar; *Mex.*: Yunir; *Singapore*: Domar; *Spain*: Duna; *Thai.*: Domar.

Pipamperone *(BAN, USAN, rINN)*

Floropipamide; McN-JR-3345; Pipamperon; Pipamperona; Pipampérone; Pipamperoni; Pipamperonum; R-3345; Пипамперон.
1-[3-(4-Fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide.
$C_{21}H_{30}FN_3O_2$=375.5
CAS — 1893-33-0.
ATC — N05AD05.
ATC Ver — QN05AD05.
UNII — 5402501F0W.

Pipamperone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipamperona; Pipamperona, hidrocloruro de; Pipampérone, Chlorhydrate de; Pipamperoni Hydrochloridum; Пипамперона Гидрохлорид.

$C_{21}H_{30}FN_3O_2.2HCl$=448.4

CAS — 2448-68-2.

ATC — N05AD05.

ATC Vet — QN05AD05.

UNII — IT085U64JB.

Profile

Pipamperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given orally as the hydrochloride for the treatment of psychoses. Doses are expressed in terms of the base; pipamperone hydrochloride 47.8 mg is equivalent to about 40 mg of pipamperone. Usual initial doses, equivalent to 40 mg of the base, have been given 2 or 3 times daily, increased gradually thereafter according to response; doses of 360 mg or more have been given daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Dipiperon; ***Denm.***: Dipiperon; ***Fr.***: Dipiperon; ***Ger.***: Dipiperon; ***Gr.***: Dipiperon; ***Neth.***: Dipiperon; ***Switz.***: Dipiperon.

Pipotiazine *(BAN, rINN)*

Pipothiazine; Pipotiatsiini; Pipotiazin; Pipotiazina; Pipotiazinum; RP-19366; Пипотиазин.

10-[3-[4-(2-Hydroxyethyl)piperidino]propyl]-*NN*-dimethylphenothiazine-2-sulphonamide; 2-[4-[3-(2-Dimethylsulphamoylphenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

$C_{24}H_{33}N_3O_3S_2$=475.7.

CAS — 39860-99-6.

ATC — N05AC04.

ATC Vet — QN05AC04.

UNII — L903J9JPYV.

Pipotiazine Palmitate *(BANM, USAN, rINNM)*

IL-19552; Palmitato de pipotiazina; Pipothiazine Palmitate; Pipotiazina, palmitato de; Pipotiazine, Palmitate de; Pipotiazini Palmitas; RP-19552; Пипотиазина Палмитат.

$C_{40}H_{63}N_3O_4S_2$=714.1

CAS — 37517-26-3.

ATC — N05AC04.

ATC Vet — QN05AC04.

UNII — 4Q3H01QRMI.

Uses and Administration

Pipotiazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain. It is used in the treatment of schizophrenia (below) and other psychoses. Pipotiazine is given orally as the base and by deep intramuscular injection as the palmitate ester; oral doses are expressed as the base and parenteral doses are expressed as the ester.

A usual oral dose of pipotiazine for the treatment of psychoses is 5 to 20 mg daily; in severe psychoses up to 30 mg daily has been given for brief periods.

The long-acting palmitate ester of pipotiazine is given by deep intramuscular injection. An initial test dose of 25 mg is followed by a further 25 to 50 mg after 4 to 7 days. The dosage is then adjusted in increments of 25 to 50 mg according to response every 4 weeks. Usual maintenance doses of 50 to 100 mg are given at average intervals of 4 weeks; the maximum recommended dose in the UK is 200 mg every 4 weeks.

Pipotiazine should be given in reduced dosage to elderly patients; a starting dose of 5 to 10 mg has been suggested for pipotiazine palmitate intramuscular injections.

Schizophrenia. A systematic review[1] concluded that depot pipotiazine palmitate appeared to be no different in terms of efficacy or adverse effects to other antipsychotics given orally or by depot injection in the treatment of schizophrenia (p. 1031.3).

1. Dinesh M, *et al.* Depot pipotiazine palmitate and undecylenate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Effects on mental function. Manic symptoms developed in a schizophrenic patient given pipotiazine palmitate. Symptoms recurred on rechallenge.[1]

1. Singh AN, Maguire J. Pipothiazine palmitate induced mania. *BMJ* 1984; 289: 734.

Pharmacokinetics

Pipotiazine palmitate is very slowly absorbed from the site of intramuscular injection. It gradually releases pipotiazine into the body and is therefore suitable for use as a depot injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Piportil L4; ***Braz.***: Piportil; ***Canad.***: Piportil L4; ***Chile***: Piportyl; ***China***: Ni Meng Shu (尼隻舒); ***Fr.***: Piportil; ***Hung.***: Piportil†; ***Irl.***: Piportil†; ***Mex.***: Piportil L4; ***NZ***: Piportil; ***Rus.***: Piportil (Пипортил)†; ***Singapore***: Piportil; ***Spain***: Lonseren; ***UK***: Piportil.

Prazepam *(BAN, USAN, rINN)*

Pratsepaami; Prazepám; Prazépam; Prazepamas; Prazepamum; W-4020; Празепам.

7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

$C_{19}H_{17}ClN_2O$=324.8

CAS — 2955-38-6.

ATC — N05BA11.

ATC Vet — QN05BA11.

UNII — Q30VCC064M.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Prazepam). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

Profile

Prazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.2). After oral doses, prazepam undergoes extensive first-pass metabolism in the liver to oxazepam (p. 1092.2) and desmethyldiazepam (nordazepam, p. 1089.3). Desmethyldiazepam is largely responsible for the pharmacological activity of prazepam. The usual oral dose for the short-term treatment of anxiety disorders (p. 1028.1) is 30 mg daily as a single nightly dose or in divided doses; in severe conditions up to 60 mg daily has been given. In elderly or debilitated patients, treatment should start with a daily dose of no more than 15 mg.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of prazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The ratio of desmethyldiazepam in plasma to that in breast milk of 5 women given prazepam 20 mg three times daily for 3 days was 9.6 from measurements 12 hours after the last dose.[2] It was estimated that a breast-fed infant of a mother on continuous prazepam therapy would ingest the equivalent of about 4% of the daily maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Brodie RR, *et al.* Concentrations of N-descyclopropylmethylprazepam in whole-blood, plasma, and milk after administration of prazepam to humans. *Biopharm Drug Dispos* 1981; 2: 59–68.

Pharmacokinetics. References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; 24: 446–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Demetrin; ***Belg.***: Lysanxia; ***Fr.***: Lysanxia; ***Ger.***: Demetrin; Mono Demetrin; ***Gr.***: Centrac; Demetonevrin; ***Irl.***: Centrax; ***Ital.***: Prazene; Trepidan; ***Neth.***: Reapam; ***Port.***: Demetrin; ***S.Afr.***: Demetrin; ***Switz.***: Demetrin; ***Thai.***: Pozapam; Prasepine†.

Prochlorperazine *(BAN, rINN)*

Chlormeprazine; Prochlorpemazine; Prochlorpérazine; Prochlorperazinum; Proclorperazina; Proklooriperatsiini; Proklorperazin; Прохлорперазин.

2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine.

$C_{20}H_{24}ClN_3S$=373.9

CAS — 58-38-8.

ATC — N05AB04.

ATC Vet — QN05AB04.

UNII — YHP6YLT61T.

Pharmacopoeias. In *US.*

USP 36: (Prochlorperazine). A clear, pale yellow, viscous liquid, sensitive to light. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in ether. Store in airtight containers. Protect from light.

Prochlorperazine Edisilate *(BANM, rINNM)*

Chlormeprazine Edisylate; Edisilato de proclorperazina; Prochlorpemazine Edisylate; Prochlorpérazine, Edisilate de; Prochlorperazine Edisylate; Prochlorperazine Ethanedisulphonate; Prochlorperazini Edisilas; Proclorperazina, edisilato de; Прохлорперазина Эдизилат.

$C_{20}H_{24}ClN_3S.C_2H_6O_6S_2$=564.1

CAS — 1257-78-9.

ATC — N05AB04.

ATC Vet — QN05AB04.

UNII — PG20W5VQZS.

Pharmacopoeias. In *US.*

USP 36: (Prochlorperazine Edisylate). A white to very light yellow odourless crystalline powder. Soluble 1 in 2 of water and 1 in 1500 of alcohol; insoluble in chloroform and in ether. Solutions in water are acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. See under Prochlorperazine Mesilate below.

Prochlorperazine Maleate *(BANM, rINNM)*

Chlormeprazine Maleate; Maleato de proclorperazina; Prochloroperazyny maleinian; Prochlorpemazine Maleate; Prochlorperazine Dihydrogen Maleate; Prochlorperazine Dimaleate; Prochlorpérazine, Maléate de; Prochlorperazin-hydrogenmaleát; Prochlorperazini Maleas; Prochlorperazin-maleinát; Prochlorperazino maleatas; Proclorperazina, maleato de; Proklooriperatsiinimaleaatti; Proklorperazinmaleat; Proklórperazin-maleát; Прохлорперазина Малеат.

$C_{20}H_{24}ClN_3S.2C_4H_4O_4$=606.1

CAS — 84-02-6.

ATC — N05AB04.

ATC Vet — QN05AB04.

UNII — 1178O1JTL6.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Prochlorperazine Maleate). A white or pale yellow, crystalline powder. Very slightly soluble in water and in alcohol. A freshly prepared saturated solution in water has a pH of 3.0 to 4.0. Protect from light.

USP 36: (Prochlorperazine Maleate). A white or pale yellow, practically odourless, crystalline powder. Practically insoluble in water; soluble 1 in 1200 of alcohol; slightly soluble in warm chloroform. Its saturated solution is acid to litmus. Store in airtight containers. Protect from light.

Prochlorperazine Mesilate *(BANM, rINNM)*

Chlormeprazine Mesylate; Mesilato de proclorperazina; Prochlorpemazine Mesylate; Prochlorperazine Dimethanesulphonate; Prochlorpérazine, Mésilate de; Prochlorperazine Mesylate; Prochlorperazine Methanesulphonate; Prochlorperazini mesilas; Prochlorperazini Mesylas; Proclorperazina, mesilato de; Прохлорперазина Мезилат.

$C_{20}H_{24}ClN_3S.2CH_3SO_3H$=566.1

CAS — 5132-55-8.

ATC — N05AB04.

ATC Vet — QN05AB04.

UNII — 531SH87H9N.

Pharmacopoeias. In *Br.*

BP 2014: (Prochlorperazine Mesilate). A white or almost white, odourless or almost odourless powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 2.0 to 3.0. Protect from light.

Incompatibility. Incompatibility has been reported between the edisilate or mesilate salts of prochlorperazine and several other compounds: these include aminophylline, amphotericin B, ampicillin sodium, aztreonam, some barbiturates, benzylpenicillin salts, calcium gluconate, cefalotin sodium, cefmetazole sodium, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, midazolam hydrochloride, and some sulfonamides. Incompat-

ibility between prochlorperazine edisilate and morphine sulfate has been attributed to phenol present in some formulations of the opioid.[1,2] Incompatibility has been reported on dilution of prochlorperazine edisilate injection with sodium chloride injection containing methyl hydroxybenzoate and propyl hydroxybenzoate as preservatives.[3] The problem did not occur with unpreserved sodium chloride or when benzyl alcohol was used as preservative. Prochlorperazine mesilate syrup has been reported to be incompatible with magnesium trisilicate mixture.[4]

1. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; 42: 2651.
2. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; 44: 67.
3. Jett S, *et al.* Prochlorperazine edisylate incompatibility. *Am J Hosp Pharm* 1983; 40: 210.
4. Greig JR. Stemetil syrup and magnesium trisilicate. *Pharm J* 1986; 237: 504.

Uses and Administration

Prochlorperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain. Prochlorperazine and its salts are widely used in the prevention and treatment of nausea and vomiting (p. 1814.3) including that associated with migraine (see Headache, below) or drug-induced emesis. They are also used for the short-term symptomatic relief of vertigo (p. 612.3) as occurs in Ménière's disease (p. 611.2) or labyrinthitis, and in the management of schizophrenia (p. 1031.3), mania (see Bipolar Disorder, p. 397.2), and other psychoses. Prochlorperazine has been used as an adjunct in the short-term management of severe anxiety (p. 1028.1).

Prochlorperazine as one of its salts may be given by various routes:

- orally as the maleate or the mesilate; the edisilate has also been given by this route
- buccally as the maleate
- parenterally as the edisilate or the mesilate

It may also be given rectally as the base.

Depending on the country or the manufacturer, doses of prochlorperazine are expressed either as the base or the salt. Prochlorperazine edisilate 7.5 mg, prochlorperazine maleate 8.1 mg, or prochlorperazine mesilate 7.6 mg are each equivalent to about 5 mg of prochlorperazine. Most doses in the UK are expressed in terms of the maleate or mesilate, while most doses in the USA are expressed in terms of the base. As a result there is a disparity in the dosage recommendations for these countries, with the doses in the USA tending to be higher.

Reduced dosage may be required in elderly patients.

For **nausea and vomiting** doses are as follows:

- in the UK, the usual *oral* dose for prevention is 5 to 10 mg of the maleate or mesilate (roughly equivalent to about 3 to 6.5 mg of the base) 2 or 3 times daily
- for the treatment of nausea and vomiting, recommended UK doses are 20 mg of the maleate or mesilate *orally* or 12.5 mg of the mesilate by deep *intramuscular* injection followed if necessary by a further dose of 10 mg given 2 hours after an oral dose or 6 hours after an intramuscular dose. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily
- in the USA, the *oral* dose for the control of nausea and vomiting is the equivalent of 5 or 10 mg of the base (as the maleate) given 3 or 4 times daily. The recommended *intramuscular* dosage is the equivalent of 5 to 10 mg of the base (as the edisilate) given every 3 to 4 hours if necessary, up to a total of 40 mg of the base daily. The *rectal* dose is 25 mg of the base given twice daily. In the management of severe nausea and vomiting the equivalent of 2.5 to 10 mg of prochlorperazine (as the edisilate) may be given by slow *intravenous* injection or infusion at a rate not exceeding 5 mg/minute; doses should not exceed 40 mg daily

For treatment of **psychoses** the following doses have been given:

- in the UK, prochlorperazine maleate or mesilate may be given in an *oral* dose of 12.5 mg twice daily for 7 days adjusted gradually to 75 to 100 mg daily according to response; some patients may be maintained on doses of 25 to 50 mg daily. The equivalent of prochlorperazine mesilate 12.5 to 25 mg two or three times daily may be given by deep *intramuscular* injection
- in the USA, prochlorperazine is given as the maleate in usual initial *oral* doses equivalent to 5 or 10 mg of the base 3 or 4 times daily adjusted according to response up to a maximum of 150 mg of base daily. In acute disturbances it may be given by deep *intramuscular* injection as the edisilate in usual doses equivalent to 10 to 20 mg of the base and repeated every 2 to 4 hours if necessary

For details of doses in children, see below.

Oral doses of 5 to 10 mg of the maleate or mesilate (or, in the USA, the equivalent of 5 mg of the base) up to 3 or 4 times daily have been used for short-term adjunctive management of **severe anxiety disorders**.

Prochlorperazine is also licensed in the UK for the treatment of **vertigo** including that due to Ménière's disease. It is given *orally* in doses of 15 to 30 mg of the maleate or mesilate daily in divided doses; after several weeks the dose may be gradually reduced to 5 to 10 mg daily. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily.

Administration in children. Owing to the risk of severe extrapyramidal reactions, prochlorperazine should be used with extreme caution in children; it is not recommended for very young children or those weighing less than 10 kg.

There are similar discrepancies with children's doses of prochlorperazine to those of adult doses, see Uses and Administration, above. The following doses are suggested in the treatment of **nausea and vomiting**:

- Where use in children is unavoidable, UK licensed product information has suggested that 250 micrograms/kg of the maleate or mesilate may be given orally 2 or 3 times daily to those aged 1 year and over for the prevention and treatment of nausea and vomiting; the intramuscular route is considered unsuitable. However, the *BNFC* suggests giving intramuscular doses, repeated up to 3 times daily if necessary, according to age as follows: 2 to 5 years, 1.25 to 2.5 mg; 5 to 12 years, 5 to 6.25 mg.
- In the USA oral and intramuscular routes are advocated for children aged 2 years and over. The usual oral antiemetic dose, given in divided doses, ranges up to 7.5 mg of the base or its equivalent daily in children weighing about 10 to 13 kg; in children 14 to 17 kg, up to 10 mg daily; from 18 to 39 kg, up to 15 mg daily. More than one day of oral antiemetic therapy is seldom necessary. The suggested intramuscular dose is the equivalent of 132 micrograms/kg of the base given as a single deep intramuscular injection of the edisilate.

In the USA, prochlorperazine is also licensed for the treatment of **schizophrenia**. The usual oral dose, given in divided doses, ranges up to 20 mg of the base or its equivalent daily in those aged 2 to 5 years, and up to 25 mg daily in children aged 6 to 12 years. It may also be given intramuscularly in similar doses to those used for nausea and vomiting.

Headache. Some phenothiazines such as prochlorperazine have been used in the control of the symptoms of severe migraine (see p. 1046.3). In comparative studies[1,2] prochlorperazine appears to have been more effective in relieving migraine headache and nausea and vomiting than metoclopramide when these drugs were given parenterally. Intravenous prochlorperazine was shown to be effective in aborting intractable migraine in children in a small uncontrolled study.[3]

1. Coppola M, *et al.* Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; 26: 541–6.
2. Jones J, *et al.* Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; 14: 262–4.
3. Kabbouche MA, *et al.* Tolerability and effectiveness of prochlorperazine for intractable migraine in children. *Pediatrics* 2001; 107: 767. Full version: http://pedlatrics.aappublications.org/cgi/content/full/107/4/e62 (accessed 28/04/04)

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Prochlorperazine may cause less sedation and fewer antimuscarinic effects but extrapyramidal effects may be more frequent.

Severe dystonic reactions have followed the use of prochlorperazine, particularly in children and adolescents. It should therefore be used with extreme care in children. In addition, in the UK, parenteral use in children is not recommended.

Local irritation has occurred after the use of buccal tablets of prochlorperazine maleate.

Effects on the cardiovascular system. Hypertension has been reported[1] in a few patients given prochlorperazine intravenously for prophylaxis of cisplatin-induced nausea and vomiting.

See also under Chlorpromazine, p. 1047.3.

1. Roche H, *et al.* Hypertension and intravenous antidopaminergic drugs. *N Engl J Med* 1985; 312: 1125–6.

Effects on the mouth. Reports of ulceration and soreness of the lip and tongue have been associated with use of prochlorperazine maleate oral tablets.[1,2] The erosive cheilitis resolved after withdrawal of prochlorperazine and recurred on rechallenge.

1. Duxbury AJ, *et al.* Erosive cheilitis related to prochlorperazine maleate. *Br Dent J* 1982; 153: 271–2.
2. Reilly GD, Wood ML. Prochlorperazine—an unusual cause of lip ulceration. *Acta Derm Venereol (Stockh)* 1984; 64: 270–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prochlorperazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

The pharmacokinetics of prochlorperazine were studied in 8 healthy subjects after doses of 6.25 and 12.5 mg intravenously, and 25 mg orally.[1] There was a marked interindividual variation in pharmacokinetics after intravenous doses but no evidence of dose-dependent pharmacokinetics; mean terminal half-lives were 6.8 hours for the higher and 6.9 hours for the lower dose. The apparent volume of distribution was very high and plasma clearance values were apparently greater than liver plasma flow, suggesting that the liver may not be the only site of metabolism. After oral doses, prochlorperazine concentrations were detectable in only 4 of the 8 subjects, due in part to a low bioavailability but also to the lack of sensitivity of the high-pressure liquid chromatographic assay used. The time to peak plasma concentration varied from 1.5 to 5 hours, and the peak concentrations varied from 1.6 to 7.6 nanograms/mL. Bioavailability was estimated to range from 0 to 16%. A low bioavailability due to high first-pass metabolism would be expected because of the high plasma clearance of prochlorperazine.

1. Taylor WB, Bateman DN. Preliminary studies of the pharmacokinetics and pharmacodynamics of prochlorperazine in healthy volunteers. *Br J Clin Pharmacol* 1987; 23: 137–42.

Buccal route. Both single- and multiple-dose studies indicated that bioavailability of prochlorperazine maleate was greater after buccal doses than when given orally.[1,2] Doses of 3 mg twice daily by the buccal route and 5 mg three times daily by mouth produced similar steady-state plasma-prochlorperazine concentrations.[1]

1. Hessell PG, *et al.* A comparison of the availability of prochlorperazine following im buccal and oral administration. *Int J Pharmaceutics* 1989; 52: 159–64.
2. Finn A, *et al.* Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. *J Clin Pharmacol* 2005; 45: 1383–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Nausetil; Procalm; Prozine; Stemetil; Stemzine; ***Canad.***: Apo-Prochlorazine; Nu-Prochlor; ***Denm.***: Stemetil; ***Fin.***: Stemetil; ***Hong Kong***: Antinaus†; Dhaperazine; Metil†; PCP†; Peratil†; Seratil; Stemetil; ***India***: Bukatel; Comptil; Emex; Emidoxyn; Emikind; Ingametil; Meditil; Nausetil; Stemetil; Vometil; ***Irl.***: Buccastem; Stemetil; ***Ital.***: Stemetil; ***Malaysia***: Dhaperazine; Lartil; Nautisol; Prochlor; Protazine; ***Neth.***: Stemetil†; ***Norw.***: Stemetil; ***NZ***: Antinaus; Buccastem; Stemetil; ***Pol.***: Chloropernazinum; ***S.Afr.***: Mitil; Scripto-Metic; Stemetil; ***Singapore***: Dhaperazine; PCP; Peratil; Prochlor; Properazine; Stemetil; ***Swed.***: Stemetil†; ***Thai.***: Prodozine; Stabil; Stemetil; ***UK***: Buccastem; Stemetil; ***USA***: Compazine†; Compro.

Multi-ingredient Preparations. ***India***: Emidoxyn Forte; Ghoom; Mizeco; Motion Plus; Neuromol; Nuroflow; ***Ital.***: Difmetre.

Pharmacopoeial Preparations

BP 2014: Prochlorperazine Buccal Tablets; Prochlorperazine Injection; Prochlorperazine Oral Solution; Prochlorperazine Tablets;

USP 36: Prochlorperazine Edisylate Injection; Prochlorperazine Maleate Tablets; Prochlorperazine Oral Solution; Prochlorperazine Suppositories.

Promazine *(BAN, rINN)*

A-145; NSC-31447; Promatsiini; Promazin; Promazina; Promazinum; Propazinum; 3276-RP; RP-3276; WY-1094; Промазин.

NN-Dimethyl-3-phenothiazin-10-ylpropylamine.

$C_{17}H_{20}N_2S$ = 284.4.

CAS — 58-40-2.

ATC — N05AA03.

ATC Vet — QN05AA03.

UNII — O9M39HTM5W.

NOTE. The code A-145 has also been used for *N*-ethylcarbaminomethyl-*L*-isoleucine, a compound investigated as an antineoplastic

Promazine Embonate *(BANM, rINNM)*

Embonato de promazina; Promazina, embonato de; Promazine, Embonate de; Promazine Pamoate; Promazini Embonas; Промазина Эмбонат.

$(C_{17}H_{20}N_2S)_2C_{23}H_{16}O_6$=957.2

ATC — N05AA03.

ATC Vet — QN05AA03.

Promazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de promazina; Promatsiinihydrokloridi; Promazina, hidrocloruro de; Promazine, Chlorhydrate de; Promazinhidroklorid; Promazinhydrochlorid; Promazin-hydrochlorid; Promazinhydroklorid; Promazini hydrochloridum; Promazino hidrochloridas; Promazyny chlorowodorek; Промазина Гидрохлорид.

$C_{17}H_{20}N_2S$,HCl=320.9

CAS — 53-60-1.

ATC — N05AA03.

ATC Vet — QN05AA03.

UNII — U16EOR79U4.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Promazine Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Very soluble in water, in alcohol, and in dichloromethane. A freshly prepared 5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Promazine Hydrochloride). A white or slightly yellow, practically odourless, crystalline powder. It oxidises upon prolonged exposure to air and acquires a pink or blue colour. Soluble 1 in 3 of water; freely soluble in chloroform. pH of a 1 in 20 solution is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between promazine hydrochloride and several other compounds: these include aminophylline, some barbiturates, benzylpenicillin potassium, chlortetracycline, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, phenytoin sodium, prednisolone sodium phosphate, and sodium bicarbonate.

Sorption. A study[1] of drug loss from intravenous delivery systems reported an 11% loss of promazine hydrochloride from solution when infused for 7 hours via a plastic infusion set, and a 59% loss after infusion for one hour from a glass syringe through silastic tubing. Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; 39: 460–7.

Stability. A study of the stability of promazine diluted to a 0.1% infusion in sodium chloride 0.9% or glucose 5% found that solutions in glucose 5% remained stable for up to 6 days at 4 degrees, and at room temperature, provided they were stored in the dark.[1] However, with sodium chloride 0.9% as the diluent, deterioration of promazine was seen 24 hours after preparation, even when stored in the dark, and after 8 hours when exposed to light. Temperature had no effect on degradation rate.

1. Tebbett IR, *et al.* Stability of promazine as an intravenous infusion. *Pharm J* 1986; 237: 172–4.

Uses and Administration

Promazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has relatively weak antipsychotic activity and is not generally used for the management of psychoses. It is mainly used for the short-term management of agitated or disturbed behaviour (p. 1030.2). It has also been given for the alleviation of nausea and vomiting (p. 1814.3). Promazine is given as the hydrochloride orally, buccally, intramuscularly, or by slow intravenous injection. Promazine has also been given orally as the embonate.

For the treatment of **agitated behaviour**, promazine hydrochloride is given in oral doses of 100 to 200 mg four times daily. It has also been given by intramuscular or slow intravenous injection in a dose of 50 mg.

A dose of 25 to 50 mg every 4 to 6 hours has been given buccally for the control of **nausea and vomiting**; it has also been given parenterally for this indication.

Promazine should be given in reduced dosage to elderly or debilitated patients; 25 mg orally of the hydrochloride initially, increasing, if necessary, to 50 mg four times daily has been suggested for the control of agitation and restlessness.

Hiccup. Promazine hydrochloride has been used in some countries for the treatment of intractable hiccup. A protocol for the management of intractable hiccups may be found under Chlorpromazine, p. 1046.3.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Pregnancy. An increased incidence of neonatal jaundice coincided with the increased use of promazine.[1] A decrease in the incidence of jaundice was noted 3 months after the total withdrawal of the drug from the hospital although restriction of its use during labour had no impact.

1. John E. Promazine and neonatal hyperbilirubinaemia. *Med J Aust* 1975; 2: 342–4.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

The pharmacokinetics of promazine appear to be generally similar to those of chlorpromazine (p. 1053.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Prazine; Sinophenin; Sparine; *Ital.*: Talofen; *Rus.*: Propazine (Пропазин); *S.Afr.*: Sparine†; *Switz.*: Prazine; *USA*: Prozine.

Pharmacopoeial Preparations
BP 2014: Promazine Injection; Promazine Tablets;
USP 36: Promazine Hydrochloride Injection; Promazine Hydrochloride Oral Solution; Promazine Hydrochloride Syrup; Promazine Hydrochloride Tablets.

Propionylpromazine

Dipropimazine; Propionilpromazina; Propiopromazine.

CAS — 3568-24-9.

UNII — Y1BCT33417.

Profile

Propionylpromazine is a phenothiazine antipsychotic that has been used for sedation and premedication in veterinary medicine.

Prothipendyl Hydrochloride *(BANM, rINNM)*

D-206; Hidrocloruro de protipendilo; Phrenotropin; Prothipendyl, Chlorhydrate de; Prothipendyli Hydrochloridum; Protipendilo, hidrocloruro de; Протипендила Гидрохлорид.

NN-Dimethyl-3-(pyrido[3,2-*b*][1,4]benzothiazin-10-yl)propylamine hydrochloride monohydrate.

$C_{16}H_{19}N_3S$,HCl,H_2O=339.9

CAS — 303-69-5 (prothipendyl); 1225-65-6 (anhydrous prothipendyl hydrochloride).

ATC — N05AX07.

ATC Vet — QN05AX07.

UNII — 7610629RVH.

Profile

Prothipendyl is an azaphenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It is given as the hydrochloride in oral doses of 40 to 80 mg two to four times daily for the treatment of psychoses (p. 1030.2) and agitation. Prothipendyl hydrochloride may also be given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Dominal; *Belg.*: Dominal; *Ger.*: Dominal.

Proxibarbal *(rINN)*

HH-184; Proksybarbal; Proxibarbalum; Proxibarbital; Прокси-барбал.

5-Allyl-5-(2-hydroxypropyl)barbituric acid.

$C_{10}H_{14}N_2O_4$=226.2

CAS — 2537-29-3.

ATC — N05CA22.

ATC Vet — QN05CA22.

UNII — F97OMS297F.

Pharmacopoeias. In *Pol.*

Profile

Proxibarbal is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used as a sedative in the management of anxiety disorders. It has also been used in the treatment of headache. However, barbiturates are not considered appropriate in the management of these conditions. Proxibarbal has been associated with severe hypersensitivity-induced thrombocytopenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Axeen; *Hung.*: Vasalgin†.

Quazepam *(BAN, USAN, rINN)*

Kvatsepaami; Kvazepam; Quazépam; Quazepamum; Sch 16134; Квазепам.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepine-2-thione.

$C_{17}H_{11}ClF_4N_2S$=386.8

CAS — 36735-22-5.

ATC — N05CD10.

ATC Vet — QN05CD10.

UNII — JF8V0828ZI.

Pharmacopoeias. In *US.*

USP 36: (Quazepam). Off-white to yellowish powder.

Uses and Administration

Quazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is given as a hypnotic in the short-term management of insomnia (p. 1033.2), in an initial oral dose of 15 mg at night; in elderly or debilitated patients and some other patients this can be reduced to 7.5 mg.

References.

1. Nishiyama T, *et al.* Effects of quazepam as a preoperative night hypnotic: comparison with brotizolam. *J Anesth* 2007; 21: 7–12.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of quazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

However, a study in 4 women given a single 15-mg dose of quazepam found that only about 0.1% of the dose was excreted over 48 hours in breast milk, as quazepam and its 2 major metabolites.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Hilbert JM, *et al.* Excretion of quazepam into human breast milk. *J Clin Pharmacol* 1984; 24: 457–62.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Quazepam is readily absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being reached in about 2 hours. It is metabolised extensively in the liver. The principal active metabolites are 2-oxoquazepam and *N*-desalkyl-2-oxoquazepam (*N*-desalkylflurazepam) which have elimination half-lives of about 39 and 73 hours, respectively, compared with a half-life of 39 hours for quazepam. Further hydroxylation occurs and quazepam is excreted in the urine and faeces mainly as conjugated metabolites.

Quazepam and its two active metabolites are more than 95% bound to plasma proteins. Quazepam and its metabolites are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Dormyl; *Jpn*: Doral; *Spain*: Quiedorm; *USA*: Doral.

Pharmacopoeial Preparations
USP 36: Quazepam Tablets.

Quetiapine Fumarate

(BANM, USAN, pINNM)

Fumarato de quetiapina; ICI-204636; Quetiapina, fumarato de; Quétiapine, Fumarate de; Quetiapini Fumaras; ZD-5077; ZM-204636; Кветиапина Фумарат.

2-[2-(4-Dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy] ethanol fumarate (2:1) salt.

$(C_{21}H_{25}N_3O_2S)_2, C_4H_4O_4$=883.1

CAS — 111974-69-7 (quetiapine); 111974-72-2 (quetiapine fumarate).

ATC — N05AH04.

ATC Vet — QN05AH04.

UNII — 2S3PL1B6UJ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of quetiapine fumarate:

Baby heroin; Susie-Q; Quell.

Uses and Administration

Quetiapine fumarate is a dibenzothiazepine atypical antipsychotic. It is reported to have affinity for serotonin ($5\text{-}HT_2$), histamine (H_1), and adrenergic (α_1 and α_2) receptors as well as dopamine D_1 and D_2 receptors. Quetiapine is used in the treatment of schizophrenia (below) and of bipolar disorder (below). It is also used for the symptomatic relief of unipolar depression (below) in patients who are refractory to, or intolerant of, antidepressants.

Quetiapine is given orally as the fumarate although doses are expressed in terms of the base; 28.8 mg of quetiapine fumarate is equivalent to about 25 mg of quetiapine.

The usual initial daily dose in **schizophrenia** is the equivalent of 50 mg of the base on day one given in 2 divided doses. UK licensed product information recommends to give 100 mg on day two, 200 mg on day three, and 300 mg on day four; daily doses are given in 2 divided doses. The dosage is then adjusted, according to response and tolerance, to a usual range of 300 to 450 mg daily, although 150 mg daily may be adequate for some patients; the maximum recommended dose is 750 mg daily. US product information states that the usual initial daily dose is increased on days two and three in steps of 50 to 150 mg, as tolerated, to a target of 300 to 400 mg daily by day four. The daily dose on the first day is given in 2 divided doses, but may be given in 3 divided doses thereafter according to tolerance. The daily dosage may be further adjusted as necessary in steps of 50 to 100 mg at intervals of not less than 2 days to a usual range similar to that licensed in the UK.

In the treatment of *acute manic episodes* associated with **bipolar disorder**, the initial dose is 100 mg on day one, 200 mg on day two, 300 mg on day three, and 400 mg on day four; daily doses are given in 2 divided doses. Further dose increases to 800 mg daily by day six should be made in steps of no greater than 200 mg daily. The dose may then be adjusted according to response and tolerance to a usual range of 400 to 800 mg daily, although, in some patients, 200 mg daily may be adequate. Quetiapine is also used for the *depressive phase* of bipolar disorder. The initial dose is 50 mg once daily at bedtime increased to 100 mg on day two, 200 mg on day three, and 300 mg on day four. The dose may be further increased to 400 mg on day five and 600 mg on day eight, if necessary. For the *maintenance treatment* of bipolar disorder, patients should be continued on the same dose on which they were stabilised.

A modified-release preparation of quetiapine is available in some countries for once-daily dosing in the treatment of schizophrenia and of bipolar disorder.

The modified-release preparation is also used as an adjunct to antidepressants in the management of **unipolar depression**. The initial dose is 50 mg once daily on days one and two, increased to the usual dose of 150 mg once daily on day three; thereafter, the dose may be increased to a maximum of 300 mg daily as necessary.

Quetiapine should be given in reduced doses to the elderly; a recommended starting dose of the immediate-release tablets is 25 mg daily, which may be increased every day in increments of 25 to 50 mg according to response. Similarly, elderly patients should be started on the lowest available dose of the modified-release preparation and titrated at a slower rate. The effective dose range is likely to be lower than in younger adults. Reduced doses are also recommended in patients with hepatic impairment, see Administration in Hepatic Impairment, below.

For details of uses and associated doses in children and adolescents, see Administration in Children, below.

Administration in children. In the USA, quetiapine is licensed for the treatment of schizophrenia in adolescents aged 13 to 17 years and, as monotherapy, for the treatment of acute manic or mixed episodes associated with bipolar disorder in those aged 10 to 17 years. For both indications, the recommended initial oral dose is the equivalent of 50 mg of the base on day one, followed by 100 mg on day two, 200 mg on day three, 300 mg on day four, and 400 mg on day five; daily doses are usually given in 2 divided doses, or if necessary in 3 divided doses according to response and tolerance. The dosage is then adjusted in steps of no greater than 100 mg, according to response and tolerance, to a usual range of 400 to 800 mg daily for schizophrenia, or 400 to 600 mg daily for bipolar disorder.

Although unlicensed in the UK for use in children and adolescents aged under 18 years, the *BNFC* suggests that quetiapine may be given, under specialist supervision, to those aged 12 years and over. For the treatment of schizophrenia, usual oral adult doses (see Use and Administration, above) may be given; a modified-release preparation may also be used for once-daily dosing. For the treatment of acute manic episodes associated with bipolar disorder, doses are similar to those licensed in the USA for this indication (see above).

Administration in hepatic impairment. Quetiapine should be given in reduced doses to patients with hepatic impairment; a recommended initial oral dose of the immediate-release tablets is 25 mg daily, increased in steps of 25 to 50 mg daily according to response. Similarly, those with hepatic impairment should be started on the lowest available dose of the modified-release preparation.

Bipolar disorder. Quetiapine is of benefit for the treatment of mania in patients with bipolar disorder (p. 397.2) and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of quetiapine-induced mania (see p. 1102.2). Quetiapine is also used in the depressive phase of bipolar disorder, and for other forms of resistant depression (below).

References.

1. Vieta E, *et al.* Quetiapine in the treatment of rapid cycling bipolar disorder. *Bipolar Disord* 2002; **4:** 335–40.
2. Delbello MP, *et al.* A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1216–23.
3. Yatham LN, *et al.* Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol* 2004; **24:** 599–606. Correction. *ibid.* 2005; **25:** 103.
4. Bowden CL, *et al.* A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 2005; **66:** 111–21.
5. Dando TM, Keating GM. Quetiapine: a review of its use in acute mania and depression associated with bipolar disorder. *Drugs* 2005; **65:** 2533–51.
6. Calabrese JR, *et al.* BOLDER Study Group. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 2005; **162:** 1351–60.
7. Thase ME, *et al.* BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 2006; **26:** 600–9. Correction. *ibid.* 2007; **27:** 51.
8. Pini S, *et al.* The role of quetiapine in the treatment of bipolar disorder. *Expert Opin Pharmacother* 2006; **7:** 929–40.
9. Khouzam HR, Singh F. Bipolar disorder: historic perspective, current pharmacologic treatment options and a review of quetiapine. *Expert Rev Neurother* 2006; **6:** 131–44.
10. Keating GM, Robinson DM. Quetiapine: a review of its use in the treatment of bipolar depression. *Drugs* 2007; **67:** 1077–94.
11. Brahm NC, *et al.* Quetiapine for acute mania in bipolar disorder. *Am J Health-Syst Pharm* 2007; **64:** 1045–53.
12. Weisler RH, *et al.* Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. *J Clin Psychiatry* 2008; **69:** 769–82.
13. DelBello MP, *et al.* A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder: *Bipolar Disord* 2009; **11:** 483–93.
14. Young AH, *et al.* EMBOLDEN I (Trial 001) Investigators. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 2010; **71:** 150–62.
15. McElroy SL, *et al.* EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 2010; **71:** 163–74.

Depression. A modified-release preparation of quetiapine is used in some countries for the management of resistant depression (p. 398.1).

References.

1. Cutler AJ, *et al.* Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. *J Clin Psychiatry* 2009; **70:** 526–39. Correction. *ibid.*; 1729.
2. Bauer M, *et al.* Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *J Clin Psychiatry* 2009; **70:** 540–9.
3. Weisler R, *et al.* Moonstone Study Group. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. *CNS Spectr* 2009; **14:** 299–313.

Parkinsonism. Quetiapine has been tried as an antipsychotic[1-4] in patients with parkinsonism (p. 889.1).

1. Fernandez HH, *et al.* Long-term outcome of quetiapine use for psychosis among Parkinsonian patients. *Mov Disord* 2003; **18:** 510–14.
2. Juncos JL, *et al.* Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. *Mov Disord* 2004; **19:** 29–35.
3. Morgante L, *et al.* Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol* 2004; **27:** 153–6. Correction. *ibid.*: 256.
4. Kurlan R, *et al.* Alzheimer's Disease Cooperative Study Group. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* 2007; **68:** 1356–63.

Schizophrenia. A systematic review[1] noted that, although quetiapine is effective for the treatment of schizophrenia (p. 1031.3), it appeared comparable with classical antipsychotics and risperidone. The incidence of extrapyramidal effects was lower with quetiapine therapy but the risk of dry mouth and somnolence was higher. Quetiapine was not found to benefit negative symptoms.

1. Srisurapanont M, *et al.* Quetiapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 30/05/05).

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) haloperidol or pimozide are commonly used but atypical antipsychotics, including quetiapine, are increasingly being tried.[1-3]

1. Mukaddes NM, Abali O. Quetiapine treatment of children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 2003; **13:** 295–9.
2. Little AE, *et al.* Quetiapine in the treatment of tic disorder. *Ann Pharmacother* 2006; **40:** 1472.
3. de Jonge JL, *et al.* Quetiapine in patients with Tourette's disorder: an open-label, flexible-dose study. *J Clin Psychiatry* 2007; **68:** 1148–50.

Adverse Effects, Treatment, and Precautions

Although quetiapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Quetiapine has been associated with a low incidence of extrapyramidal symptoms but tardive dyskinesia may occur after long-term treatment. Rises in prolactin concentrations may be less than with chlorpromazine.

The most frequent adverse effects with quetiapine are somnolence, headache, and dizziness. Other common adverse effects include weight gain, particularly during early treatment, and rises in plasma-triglyceride and total cholesterol concentrations. Mild asthenia, anxiety, irritability, fever, rhinitis, peripheral oedema, increased appetite, constipation, dyspepsia, dry mouth, and raised liver enzyme values are also relatively common. Orthostatic hypotension associated with dizziness, tachycardia, and syncope has been reported, particularly during initial dose-titration. Prolongation of QT interval is rarely significant with quetiapine. Venous thromboembolism has been reported rarely. Hyperglycaemia and exacerbation of pre-existing diabetes have been reported rarely. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of developing, diabetes. Neuroleptic malignant syndrome is rare with quetiapine. Leucopenia, neutropenia, thrombocytopenia, and eosinophilia have also been reported, as have reduced plasma-thyroid hormone concentrations. There have been rare reports of seizures, hypersensitivity reactions including angioedema, and priapism.

Asymptomatic changes in the lens of the eye have occurred in patients during long-term treatment with quetiapine; cataracts have developed in *dogs* during chronic dosing studies. In the USA, it is recommended that patients should have an eye examination to detect cataract formation when starting therapy with quetiapine and every 6 months during treatment.

Adverse effects such as increased appetite, extrapyramidal symptoms, and rises in prolactin concentrations may occur at a higher frequency in children and adolescents than in adults. Increases in blood pressure have been reported in children and adolescents, and blood pressure should be measured at the beginning of, and periodically during, treatment with quetiapine.

Quetiapine should be used with caution in patients with hepatic or renal impairment, with cardiovascular disease or other conditions predisposing to hypotension, with cerebrovascular disease, or with a history of seizures or conditions that lower the seizure threshold.

When quetiapine is used for the depressive phase in bipolar disorder or for unipolar depression, patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see Bipolar Disorder, p. 397.2 and Depression, p. 398.1.

Quetiapine may affect the performance of skilled tasks including driving.

Gradual withdrawal of quetiapine is recommended because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses, with abrupt cessation.

Abuse. References to the abuse of quetiapine.

1. Pierre JM, *et al.* Intranasal quetiapine abuse. *Am J Psychiatry* 2004; 161: 1718.
2. Hussain MZ, *et al.* Intravenous quetiapine abuse. *Am J Psychiatry* 2005; 162: 1755–6.
3. Waters BM, Joshi KG. Intravenous quetiapine-cocaine use ("Q-ball"). *Am J Psychiatry* 2007; 164: 173–4.
4. Morin AK. Possible intranasal quetiapine misuse. *Am J Health-Syst Pharm* 2007; 64: 723–5.
5. Reeves RR, Brister JC. Additional evidence of the abuse potential of quetiapine. *South Med J* 2007; 100: 834–6.
6. Paparrigopoulos T, *et al.* Quetiapine: another drug with potential for misuse? A case report. *J Clin Psychiatry* 2008; 69: 162–3.
7. Murphy D, *et al.* Addictive potential of quetiapine. *Am J Psychiatry* 2008; 165: 918.
8. Tcheremissine OV. Is quetiapine a drug of abuse? Reexamining the issue of addiction. *Expert Opin Drug Safety* 2008; 7: 739–48.

Breast feeding. In a case report[1] of a mother receiving oral quetiapine 200 mg daily, the maximum concentration of the drug in breast milk an hour after the dose was reported to be 62 micrograms/litre; the mean concentration over 6 hours was 13 micrograms/litre. The authors concluded that the breast-fed infant would ingest, at maximum, the daily equivalent of 0.43% of the weight-adjusted maternal dose. Follow-up at 4.5 months reported no adverse effects in the infant, who had been breast fed from 8 weeks of age.

Licensed product information recommends that patients receiving quetiapine should not breast feed.

1. Lee A, *et al.* Excretion of quetiapine in breast milk. *Am J Psychiatry* 2004; 161: 1715–16.

Effects on the blood. There have been reports of leucopenia,[1] neutropenia,[2] and pancytopenia[3] associated with quetiapine therapy; all 3 patients improved when the drug was stopped. Thrombotic thrombocytopenic purpura has also been reported in a patient who received quetiapine on 2 separate occasions 2 years apart.[4] From December 1997 to October 2006, Health Canada[5] had received 11 reports of thrombocytopenia associated with quetiapine, 6 of which were associated with quetiapine alone. In one of these 6 cases, thrombocytopenia recurred 3 months after restarting quetiapine, which had stopped for 1 month.

1. Clark N, *et al.* Quetiapine and leukopenia. *Am J Psychiatry* 2001; 158: 817–18.
2. Croarkin P, Rayner T. Acute neutropenia in a patient treated with quetiapine. *Psychosomatics* 2001; 42: 368.
3. Iraqi A. A case report of pancytopenia with quetiapine use. *Am J Geriatr Psychiatry* 2003; 11: 694.
4. Huynh M, *et al.* Thrombotic thrombocytopenic purpura associated with quetiapine. *Ann Pharmacother* 2005; 39: 1346–8.
5. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; 17 (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2_e.pdf (accessed 09/04/08)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.

1. Brecher M, *et al.* Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry* 2007; 68: 597–603.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including quetiapine, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Further references for such effects associated with quetiapine use are given below.

1. Koller EA, *et al.* A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. *J Clin Psychiatry* 2004; 65: 857–63.
2. Takahashi M, *et al.* Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. *Pharmacopsychiatry* 2005; 38: 183–4.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

Effects on the pancreas. From December 1997 to October 2006, Health Canada[1] had received 9 reports of pancreatitis associated with quetiapine, 5 of which were associated with quetiapine alone. One patient was reported to have developed severe haemorrhagic pancreatitis, and another, necrotising pancreatitis. One report described pancreatitis occurring on two separate occasions in the patient.

1. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; 17 (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 26/07/10)

Effects on the respiratory system. Hyperventilation and respiratory alkalosis have been reported with quetiapine use.[1] Acute respiratory failure developed[2] in a 92-year-old woman with a history of chronic obstructive pulmonary disease who was given a single 50-mg dose of quetiapine.

1. Shelton PS, *et al.* Hyperventilation associated with quetiapine. *Ann Pharmacother* 2000; 34: 335–7.
2. Jabeen S, *et al.* Acute respiratory failure with a single dose of quetiapine fumarate. *Ann Pharmacother* 2006; 40: 559–62.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Mania. Although it is used in the treatment of bipolar disorder, quetiapine has been associated with mania. In one report, a 26-year-old man with schizophrenia developed manic symptoms after starting treatment with quetiapine; the symptoms resolved when quetiapine was withdrawn.[1]

1. Lykouras L, *et al.* Manic symptoms associated with quetiapine treatment. *Eur Neuropsychopharmacol* 2003; 13: 135–6.

Overdosage. Hypotension, tachycardia, and somnolence were the main clinical events seen in a patient who had taken an overdose of 3 g of quetiapine.[1] Tachycardia of an unexpectedly long duration was also noted. Management was symptomatic, including maintenance of fluids. Asymptomatic prolongation of the QT interval was seen in another patient who had taken a 2-g overdose of quetiapine.[2] Her treatment regimen also included risperidone, and the authors warned that considerable QT interval prolongation may occur when patients overdose on quetiapine while taking therapeutic doses of risperidone.

A subsequent report[3] has described a case series of 18 patients who took from 500 mg to 24 g of quetiapine either alone (6 patients) or with other drugs (12). Quetiapine overdosage was mainly associated with CNS and respiratory depression and sinus tachycardia. Four of the 18 patients required mechanical ventilation but no deaths occurred. The corrected QT interval, but not the QT interval, was prolonged, but apart from sinus tachycardia no patient had a dysrhythmia. Seizures occurred in 2 patients and delirium in 3. The patient who took 24 g of quetiapine was found to have had a peak blood concentration of 20.48 micrograms/mL. She had presented 1.5 hours after ingestion and was intubated and treated with gastric lavage followed by activated charcoal. About 2.5 hours later she had a generalised tonic-clonic seizure. The patient was discharged after 40 hours without sequelae. Another analysis[4] considered 14 cases of overdose, the amounts varying from 1.2 to 18 g; there appeared to be no correlation between the amount taken and the serum concentration, nor was severity of intoxication necessarily correlated with greater intake. Toxicity was generally mild, with tachycardia and somnolence as the main presenting symptoms; there were no fatalities.

1. Beelen AP, *et al.* Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. *Hum Exp Toxicol* 2001; 20: 215–19.
2. Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. *Clin Pharmacol Ther* 2000; 68: 92–7.
3. Balit CR, *et al.* Quetiapine poisoning: a case series. *Ann Emerg Med* 2003; 42: 751–8.
4. Hunfeld NG, *et al.* Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. *Ther Drug Monit* 2006; 28: 185–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quetiapine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics, including quetiapine, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by quetiapine. Quetiapine should be used with caution in patients also receiving antihypertensives or drugs that prolong the QT interval. Quetiapine may antagonise the actions of dopaminergics such as levodopa.

CYP3A4 is the main isoenzyme responsible for cytochrome P450-mediated metabolism of quetiapine and it should be used with caution, if at all, with potent inhibitors of CYP3A4 such as erythromycin, fluconazole, itraconazole, and ketoconazole; lower doses of quetiapine are recommended when given with such drugs. Conversely, enzyme inducers such as carbamazepine and phenytoin may decrease the plasma concentrations of quetiapine, and higher doses of quetiapine may be necessary. Thioridazine has also been reported to increase the clearance of quetiapine.

Antibacterials. In a study involving 19 Chinese patients with schizophrenia taking quetiapine 200 mg twice daily, adding *erythromycin* 500 mg three times daily increased the peak plasma concentration, area under the concentration-time curve, and terminal elimination half-life of quetiapine by 68, 129, and 92%, respectively. Reductions in plasma concentrations of the metabolites of quetiapine suggested that erythromycin had probably inhibited quetiapine's metabolism by the cytochrome P450 isoenzyme CYP3A4. Modification of dosage was recommended in this patient group taking these two drugs together.[1]

1. Li K-Y, *et al.* Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005; 60: 791–5.

Antipsychotics. For a report of asymptomatic QT prolongation associated with quetiapine in a patient also receiving *risperidone*, see under Overdosage, above.

Pharmacokinetics

Quetiapine is well absorbed after oral doses and widely distributed throughout the body. Peak plasma concentrations occur in about 1.5 hours. It is about 83% bound to plasma proteins. Quetiapine is extensively metabolised in the liver by sulfoxidation mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and by oxidation. It is excreted mainly as inactive metabolites with about 73% of a dose appearing in the urine and about 20% in the faeces. The elimination half-life has been reported to be about 6 to 7 hours.

It is distributed into breast milk.

References.

1. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 2001; 40: 509–22.
2. Jaskiw GE, *et al.* Pharmacokinetics of quetiapine in elderly patients with selected psychotic disorders. *Clin Pharmacokinet* 2004; 43: 1025–35. Correction. *ibid.*; 1178.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atipina; Biatrix; Dominium; Etiasel; Inquetia; Kemoter; Quepaz; Quetiaros; Quetiazic; Rostrum; Seroquel; Vesparax; ***Austral.***: Sequase; Seronia; Seroquel; Syquet; ***Austria***: Quetialan; Seroquel; ***Belg.***: Seroquel; ***Braz.***: Kitapen; Neotiapim; Querok; Queropax; Quetipin; Quetros; Seroquel; ***Canad.***: Seroquel; ***Chile***: Asicot; Gofyl; Norsic; Quetiazic; Quetidin; Qutipin; Seroquel; ***China***: QiWei (启维); Seroquel (思瑞康); Shu Si (舒思); ***Cz.***: Derin; Equeta; Geldoren; Hedonin; Ketilept; Kventiax; Nantarid; Quepita†; Quepsan; Questax; Quetifi†; Quetin†; Quetrop; Resirentin; Seratio; Seroquel; Stadaquel; Taiqutabs; ***Denm.***: Alzen; Generiapin†; Lobarr†; Loplive†; Loquen†; Mylaquel†; Nantarid; Quelan; Quemed; Quemyl†; Quetastad; Queteper; Quetilis; Quetiratio†; Seresano; Seroquel; Setinin; Stadaquel; Symquel; Tiaquin; ***Fin.***: Ketipinor; Seroquel; ***Fr.***: Xeroquel; ***Ger.***: Seroquel; ***Gr.***: Quepin; Seroquel; ***Hong Kong***: Seroquel; ***Hung.***: Equepin; Ketilept; Kventiax; Lantiapin†; Nantarid; Resirentin; Seroquel; Setinin; ***India***: Quel; Seroquin; Socalm; ***Indon.***: Seroquel; ***Irl.***: Notiabolfen; Quelor†; Quetex; Seropia; Seroquel; Seroquin†; Setinin; Tevaquel; ***Israel***: Seroquel; ***Ital.***: Queteper; Seroquel; ***Jpn***: Seroquel; ***Malaysia***: Ketipinor; Seroquel; ***Mex.***: Seroquel; ***Neth.***: Derin†; Gentiapin; Kefrenex†; Kwetaplex; Quentapil; Quetex; Quetiafair; Quetrop; Seroquel; ***Norw.***: Seroquel; ***NZ***: Quetapel; Seroquel; ***Philipp.***: Ketilept; Q-win; Seroquel; ***Pol.***: Bonogren; Etiagen; Geldoren; Gentiapin; Kefrenex; Ketilept; Ketipinor; Ketrel; Kventiax; Kwetaplex; Kwetinor; Loquen; Nantarid; Poetra; Quentapil; Quetiser; Seroquel; Setinin; Symquel; Vorta; ***Port.***: Alzen; Ketiron†; Neuroracet†; Pinapaz†; Raikar†; Seroquel; Viketo†; ***Rus.***: Ketilept (Кетилепт); Kventiax (Квентиакс); Lacvel (Лаквель); Nantarid (Нантарид); Seroquel (Сероквель); ***S. Afr.***: Dopaquel; Quetoser; Serez; Seroquel; Truvalin; ***Singapore***: Ketipinor; Seroquel; ***Spain***: Ilufren; Psicotric; Qudix; Quentiax; Quetiamylan; Rocoz; Seroquel; ***Swed.***: Seroquel; ***Switz.***: Sequase; Seroquel; ***Thai.***: Neutapin; Quantia; Seroquel; ***Turk.***: Cedrina; Gyrex; Ketya; Piquet; Serex; Seroquel; ***UK***: Seotiapim; Seroquel; Sondate; ***Ukr.***: Ketilept (Кетилепт); Quetiron (Кветирон); Seroquel (Сероквель); ***USA***: Seroquel; ***Venez.***: Seroquel.

Raclopride *(BAN, rINN)*

A-40664 (raclopride tartrate); FLA-870; Raclopridă; Raclopridium; Raclopridum; Rakloprid; Raklopridi; Раклоприд.

(*S*)-3,5-Dichloro-*N*-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide.

$C_{15}H_{20}Cl_2N_2O_3$=347.2

CAS — 84225-95-6 (raclopride); 98185-20-7 (raclopride tartrate).

UNII — 430K3SOZ7G.

Profile

Raclopride is a substituted benzamide related to sulpiride (p. 1107.3). It has been investigated for the treatment of psychoses. Since it binds selectively and with high affinity to D_2 dopaminergic receptors, raclopride labelled with carbon-11 has been tried as a tracer in computerised tomographic studies of neurological disorders associated with dysfunction of brain D_2 dopaminergic receptors.

Ramelteon *(BAN, USAN, rINN)*

Ramelteón; Ramelteon; Ramelteonum; TAK-375; Рамельтеон.

(-)-*N*-[2-[(8*S*)-1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl]ethyl]propanamide.

$C_{16}H_{21}NO_2$=259.3

CAS — 196597-26-9.

ATC — N05CH02.

ATC Vet — QN05CH02.

UNII — 901AS54I69.

Profile

Ramelteon is a melatonin receptor agonist used as a hypnotic in the management of insomnia (p. 1033.2), particularly in patients who have difficulty falling asleep. The usual oral dose is 8 mg taken within 30 minutes of bedtime; it should not be taken with, or immediately after, a high-fat meal.

Ramelteon is not recommended for patients with severe hepatic impairment; it should be used with caution in those with moderate impairment.

Ramelteon is metabolised mainly via the cytochrome P450 isoenzyme CYP1A2 and therefore it should not be used with fluvoxamine, a potent inhibitor of this isoenzyme; it should also be used with caution in patients taking other drugs that inhibit this isoenzyme.

Severe anaphylactic or anaphylactoid reactions have been reported rarely. Hallucinations and behavioural changes such as bizarre behaviour, agitation, and mania have also been reported; amnesia and anxiety may occur unpredictably. Complex sleep-related behaviours, such as eating or driving while asleep, have been associated with ramelteon therapy; the risk of such behaviour is increased when taken with alcohol or other CNS depressants.

Reviews.

1. Reynoldson JN, *et al.* Ramelteon: a novel approach in the treatment of insomnia. *Ann Pharmacother* 2008; **42**: 1262–70.
2. Simpson D, Curran MP. Ramelteon: a review of its use in insomnia. *Drugs* 2008; **68**: 1901–19.
3. Pandi-Perumal SR, *et al.* Ramelteon: a review of its therapeutic potential in sleep disorders. *Adv Therapy* 2009; **26**: 613–26.
4. Miyamoto M. Pharmacology of ramelteon, a selective MT_1/MT_2 receptor agonist: a novel therapeutic drug for sleep disorders. *CNS Neurosci Ther* 2009; **15**: 32–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Rozerem; *Jpn*: Rozerem; *Philipp.*: Rozerem; *USA*: Rozerem.

Rilmazafone Hydrochloride *(rINNM)*

Hidrocloruro de rilmazafona; Rilmazafone, Chlorhydrate de; Rilmazafoni Hydrochloridum; 450191-S; Рильмазафона гидрохлорид.

5-[(2-Aminoacetamido)methyl]-1-[4-chloro-2-(o-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide hydrochloride dihydrate.

$C_{21}H_{20}Cl_2N_6O_3.HCl.2H_2O$=547.8

CAS — 99593-25-6 (rilmazafone); 85815-37-8 (anhydrous rilmazafone hydrochloride).

UNII — 25T258X8BV.

Profile

Rilmazafone hydrochloride is a hypnotic and sedative used in the short-term treatment of insomnia (p. 1033.2) in usual oral doses of 1 to 2 mg at bedtime; it is also used in similar doses as a premedicant (see Anaesthesia, p. 1899.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Rhythmy.

Risperidone *(BAN, USAN, rINN)*

R-64766; Risperidon; Risperidona; Risperidonas; Rispéridone; Risperidoni; Risperidonum; Riszperidon; Rysperydon; Рисперидон.

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methylpyrido[1,2-*a*]pyrimidin-4-one.

$C_{23}H_{27}FN_4O_2$=410.5

CAS — 106266-06-2.

ATC — N05AX08.

ATC Vet — QN05AX08.

UNII — L6UH7ZF8HC.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Risperidone). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute acid solutions. Protect from light.

USP 36: (Risperidone). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in dichloromethane.

Uses and Administration

Risperidone is a benzisoxazole atypical antipsychotic, reported to be an antagonist at dopamine D_2, serotonin (5-HT_2), adrenergic (α_1 and α_2), and histamine (H_1) receptors. It is given orally for the treatment of schizophrenia (p. 1104.2) and in the short-term treatment of acute manic or mixed episodes associated with bipolar disorder (p. 1104.1). It is also given orally for the short-term (up to 6 weeks) treatment of persistent aggression (see Disturbed Behaviour, p. 1104.1) in patients with moderate to severe Alzheimer's disease unresponsive to non-pharmacological therapies and when there is risk of harm to self or others. Risperidone may be given by deep intramuscular injection for maintenance therapy in patients with schizophrenia tolerant to oral antipsychotics, or with bipolar disorder.

For **schizophrenia**, the usual initial oral dose of risperidone is 2 mg daily; this may be increased to 4 mg daily on the second day, and subsequently adjusted as required in steps of 1 or 2 mg according to tolerance, at intervals of not less than 24 hours. Most patients benefit from doses of 4 to 6 mg daily. Risperidone may be given once daily or in 2 divided doses. Extrapyramidal symptoms may be more likely with doses above 10 mg daily; US licensed product information does not recommend daily doses above 6 mg if divided into 2 doses, although higher doses are permitted if given as a single dose. The maximum recommended dose is 16 mg daily.

An initial oral dose of 500 micrograms twice daily slowly increased in steps of 500 micrograms twice daily, if necessary, to a dose of 1 to 2 mg twice daily is recommended for elderly patients with schizophrenia.

The long-acting formulation of risperidone should be given by deep intramuscular injection every 2 weeks. Patients with no history of risperidone use should be given risperidone orally for several days to assess tolerability. Treatment may then be started as follows:

- patients not stabilised on oral risperidone: 25 mg every 2 weeks
- patients stabilised on oral risperidone for at least 2 weeks in doses of 4 mg daily or less: 25 mg every 2 weeks
- patients stabilised on oral risperidone for at least 2 weeks in doses above 4 mg daily: 37.5 mg every 2 weeks

Oral risperidone should be continued for the first 3 weeks after the first injection.

Dose increases of 12.5 mg may be considered at least 4 weeks after the previous adjustment up to a maximum of 50 mg every 2 weeks; the clinical effects of a dose adjustment may not be seen for at least 3 weeks after the change.

For the treatment of *mania* in **bipolar disorder**, a recommended initial oral dose is 2 to 3 mg once daily. Dosage adjustments of 1 mg daily may be made at intervals of not less than 24 hours up to a total of 6 mg daily. The initial dosage regimen in elderly patients should be reduced as for schizophrenia (see above). In the USA, the long-acting injection may be given by deep intramuscular injection for *maintenance therapy* in a dose of 25 mg every 2 weeks; some patients may benefit from a higher dose of 37.5 or 50 mg.

For the treatment of **persistent aggression** in Alzheimer's disease, the usual initial oral dose is 250 micrograms twice daily. Dosage adjustments of 250 micrograms twice daily may be made no more frequently than every other day if required. The optimum dose for most patients is 500 micrograms twice daily although some may need up to 1 mg twice daily.

Reduced doses are recommended in patients with hepatic or renal impairment, see Administration in Hepatic or Renal Impairment, p. 1104.1.

For details of uses and associated doses in children and adolescents, see Administration in Children and Disturbed Behaviour, below and p. 1104.1, respectively.

Action. Risperidone is described as an atypical antipsychotic; although it has a lower propensity to produce parkinsonism, dystonias and akathisias have been reported.[1] (See also Extrapyramidal Disorders, p. 1105.2.) The traditional hypothesis is that antipsychotics work through inhibition of dopamine D_2 receptors and that extrapyramidal adverse effects result from blockade of D_2 receptors in the striatum (see p. 1046.1). Like clozapine, risperidone has a high affinity for 5-HT_2 receptors and, like haloperidol, it has a high affinity for dopamine D_2 receptors. Risperidone also binds to alpha-adrenergic and histamine H_1 sites. It is unclear whether risperidone's antipsychotic effect is due to activity at dopamine D_2 receptors or at another site. It has been suggested[1] that other potent effects of risperidone may be counterbalancing the D_2 activity to produce its atypicality.

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; **164**: 141–8.

Administration in children. In the USA, risperidone is licensed for the treatment of schizophrenia in adolescents aged 13 to 17 years, acute manic or mixed episodes associated with bipolar disorder in children and adolescents aged 10 to 17 years, and irritability associated with autistic disorder in those aged 5 to 17 years. In the UK, risperidone is licensed for the short-term (up to 6 weeks) treatment of persistent aggression in conduct disorder in children and adolescents aged 5 to 18 years with subaverage intellectual functioning or mental retardation; specialist supervision is recommended.

For **schizophrenia** or **mania**, an initial oral dose of 500 micrograms is given once daily in the morning or in the evening. This may be increased in steps of 0.5 or 1 mg according to tolerance, at intervals of not less than 24 hours, to a dose of 3 mg daily for schizophrenia or 2.5 mg daily for mania. The maximum recommended dose for both indications is 6 mg daily. The total daily dose may be given in 2 divided doses to those who have persistent somnolence. Although unlicensed in the UK, the *BNFC* suggests that it may be used in those aged 12 years and over for the oral treatment of acute and chronic psychoses in doses similar to those used in the treatment of schizophrenia in adults (see Uses and Administration, above); for the short-term treatment of acute manic episodes associated with bipolar disorder, the *BNFC* recommends doses similar to those licensed for this indication in the USA (see above).

For the treatment of **irritability associated with autistic disorder**, the following oral doses are given once daily or in 2 divided doses according to body-weight:

- 15 to <20 kg: the usual initial daily dose is 250 micrograms; this may be increased to 500 micrograms daily after at least 4 days and subsequently adjusted as required in steps of 250 micrograms, generally at intervals of no less than 2 weeks
- 20 kg and over: the usual initial daily dose is 500 micrograms; this may be increased to 1 mg daily after at least 4 days and subsequently adjusted as required in steps of 500 micrograms, generally at intervals of no less than 2 weeks
- The maximum recommended dose, regardless of body-weight, is 3 mg daily
- For those who have persistent somnolence, the total daily dose may be given as a single dose at bedtime, or in 2 divided doses, or in a reduced dose

The *BNFC* suggests that risperidone may be used in children over 5 years old for the short-term treatment of severe aggression in autism. Doses are similar to those licensed for autistic disorders in the USA (see above) although the maximum daily dose may differ, those recommended by the *BNFC* are: 1 mg in those weighing 15 to 20 kg, 2.5 mg in those under 45 kg, and 3 mg in those over 45 kg.

For further details on the use of risperidone in children with autism see Disturbed Behaviour, p. 1104.1.

In the treatment of **persistent aggression in conduct disorder**, the following oral doses are given once daily according to body-weight:

- under 50 kg: the usual initial dose is 250 micrograms daily, subsequently adjusted in steps of 250 micrograms no more frequently than every other day if required; the optimum dose for most patients is 500 micrograms daily although some may benefit from 250 micrograms daily whilst others may need 750 micrograms daily
- 50 kg and over: the usual initial dose is 500 micrograms daily, subsequently adjusted in steps of 500 micrograms no more frequently than every other day if required; the optimum dose for most patients is 1 mg daily although some may benefit from 500 micrograms daily whilst others may need 1.5 mg daily

Administration in hepatic or renal impairment. UK licensed product information recommends that initial and consecutive oral doses of risperidone should be halved in patients with hepatic or renal impairment irrespective of the indication. In the USA, licensed information recommends, for those with severe impairment, an initial oral dose of 500 micrograms twice daily, slowly increased thereafter in steps of 500 micrograms (or less) twice daily, if necessary; above doses of 1.5 mg twice daily, increases should be made at intervals of at least 1 week.

Patients who tolerate an oral dose of risperidone of at least 2 mg daily may be switched to the long-acting formulation of risperidone; a dose of 25 mg by deep intramuscular injection every 2 weeks is recommended. Alternatively, an initial dose of 12.5 mg by deep intramuscular injection may be given.

AIDS. Risperidone was used successfully to control HIV- or AIDS-related psychosis in 21 patients, some of whom also had manic symptoms.[1] No extrapyramidal symptoms were reported during treatment. However, for reports suggesting that risperidone can induce or exacerbate manic symptoms in patients with schizoaffective disorders, see under Mania in Adverse Effects, p. 1105.3. For an interaction between risperidone and antiretroviral therapy in a patient with AIDS, see under Interactions, p. 1106.1.

1. Singh AN, *et al.* Treatment of HIV-related psychotic disorders with risperidone: a series of 21 cases. *J Psychosom Res* 1997; **42:** 489–93.

Anxiety disorders. Although there have been anecdotal reports[1,2] of improvement after the addition of risperidone to treatment in patients with obsessive-compulsive disorder refractory to conventional treatment, there has also been a report[3] of a patient whose obsessive-compulsive behaviour recurred when he was treated with risperidone for tardive dyskinesia.

1. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry* 1995; **56:** 423–9.
2. McDougle CJ, *et al.* Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. *J Clin Psychiatry* 1995; **56:** 526–8.
3. Remington G, Adams M. Risperidone and obsessive-compulsive symptoms. *J Clin Psychopharmacol* 1994; **14:** 358–9.

Bipolar disorder. Risperidone is of benefit for the treatment of mania, including in patients with bipolar disorder (p. 397.2), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of risperidone-induced mania (see p. 1105.3).

References.

1. Segal J, *et al.* Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clin Neuropharmacol* 1998; **21:** 176–80.
2. Sachs GS, *et al.* Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* 2002; **159:** 1146–54.
3. Yatham LN, *et al.* Mood stabilisers plus risperidone or placebo in the treatment of acute mania: international, double-blind, randomised controlled trial. *Br J Psychiatry* 2003; **182:** 141–7. Correction. *ibid.*; 369.
4. Hirschfeld RM, *et al.* Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry* 2004; **161:** 1057–65.
5. Nguyen LN, Guthrie SK. Risperidone treatment of bipolar mania. *Ann Pharmacother* 2006; **40:** 674–82.
6. Rendell JM, *et al.* Risperidone alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
7. Deeks ED. Risperidone long-acting injection: in bipolar I disorder. *Drugs* 2010; **70:** 1001–12.

Disturbed behaviour. Risperidone has been tried[1-4] in the management of behavioural disturbances in **elderly patients with dementia** (p. 1030.2); however, such use has been associated with an increased risk of death (see the Elderly, under Adverse Effects, p. 1105.1). Furthermore, despite anecdotal reports[5] of efficacy in patients with Lewy-body dementia, other reports[6] suggest that these patients are likely to be just as sensitive to risperidone as to classical antipsychotics (see the Elderly in Precautions for Chlorpromazine, p. 1051.1). Nevertheless, risperidone is licensed in the UK for the short-term treatment of persistent aggression in patients with moderate to severe Alzheimer's disease unresponsive to non-pharmacological therapies and when there is risk of harm to self or others; for details of doses see Uses and Administration, p. 1103.2.

There is evidence[7-12] that risperidone may be effective in reducing behavioural disturbances in **children with autism** (see Disturbed Behaviour, p. 1030.2), but it appears to have little effect on core symptoms, and it has been pointed out that the marked hyperprolactinaemia induced by risperidone could lead to hypogonadism, and deleterious effects on adolescent bones.[13] A systematic review[14] concluded that risperidone may be of some benefit for symptoms such as hyperactivity, irritability, repetition, and social withdrawal although this must be weighed against the risk of adverse effects, notably weight gain. The authors noted that only 3 studies were analysed, including 1 that was carried out in adults, and the data available were limited; further studies were considered warranted. Nonetheless, in some countries, including the USA, risperidone is licensed for the treatment of irritability associated with autistic disorder in children and adolescents aged 5 to 16 years; for details of doses see Administration in Children, p. 1103.3.

Risperidone may also be effective in reducing aggressive symptoms in children of subaverage intellect with **conduct disorder**;[15] for details of doses, see above.

1. De Deyn PP, *et al.* A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 1999; **53:** 946–55.
2. Fabsetti AE. Risperidone for control of agitation in dementia patients. *Am J Health-Syst Pharm* 2000; **57:** 862–70.
3. Katz IR, *et al.* Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. *J Clin Psychiatry* 1999; **60:** 107–15.
4. Brodaty H, *et al.* A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* 2003; **64:** 134–43.
5. Allen RL, *et al.* Risperidone for psychotic and behavioural symptoms in Lewy body dementia. *Lancet* 1995; **346:** 185.
6. McKeith IG, *et al.* Neuroleptic sensitivity to risperidone in Lewy body dementia. *Lancet* 1995; **346:** 699.
7. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347:** 314–21.
8. Shea S, *et al.* Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Abstract: *Pediatrics* 2004; **114:** 1329. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/5/e634 (accessed 15/01/07)
9. Reyes M, *et al.* A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry* 2006; **163:** 402–10.
10. Reyes M, *et al.* Long-term safety and efficacy of risperidone in children with disruptive behaviour disorders: results of a 2-year extension study. *Eur Child Adolesc Psychiatry* 2006; **15:** 97–104.
11. Chavez B, *et al.* Role of risperidone in children with autism spectrum disorder. *Ann Pharmacother* 2006; **40:** 909–16.
12. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Pediatr Drugs* 2007; **9:** 343–54.
13. Valiquette G. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347:** 1890–1.
14. Jesner OS, *et al.* Risperidone for autism spectrum disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 10/04/08).
15. LeBlanc JC, *et al.* Risperidone reduces aggression in boys with a disruptive behaviour disorder and below average intelligence quotient: analysis of two placebo-controlled randomized trials. *Int Clin Psychopharmacol* 2005; **20:** 275–83.

Dystonias. Antipsychotics are sometimes useful in the treatment of idiopathic dystonia (p. 903.3) in patients who have failed to respond to treatment with levodopa or antimuscarinics, but, as with classical antipsychotics, there is the risk of adding drug-induced extrapyramidal effects to the dystonia. Risperidone has been reported to be of benefit in a few patients with idiopathic segmental dystonia partly insensitive to haloperidol.[1]

1. Zuddas A, Cianchetti C. Efficacy of risperidone in idiopathic segmental dystonia. *Lancet* 1996; **347:** 127–8.

Parkinsonism. There have been conflicting reports of the use of risperidone as an antipsychotic in a small number of patients with Parkinson's disease (see also Disturbed Behaviour, p. 1030.2). While some patients found that risperidone ameliorated levodopa-induced hallucinations without worsening extrapyramidal symptoms,[1,2] others reported that risperidone produced a substantial worsening of symptoms.[2,3]

1. Meco G, *et al.* Risperidone for hallucinations in levodopa-treated Parkinson's disease patients. *Lancet* 1994; **343:** 1370–1.
2. Leopold NA. Risperidone treatment of drug-related psychosis in patients with parkinsonism. *Mov Disord* 2000; **15:** 301–4.
3. Ford B, *et al.* Risperidone in Parkinson's disease. *Lancet* 1994; **344:** 681.

Schizophrenia. Risperidone is claimed to produce a relatively low incidence of extrapyramidal effects and to have efficacy against both positive and negative symptoms of schizophrenia (p. 1031.3). Most of the earlier studies compared risperidone with haloperidol but, of these, some of the major studies[1-3] were criticised for potential methodological flaws[4,5] and it was difficult to determine any difference in efficacy including effect on negative symptoms. A later systematic review[6] suggested that risperidone's benefits over haloperidol or other classical antipsychotics were marginal; although it did appear to reduce the risk of extrapyramidal effects compared with haloperidol, the latter produces a relatively high incidence of such effects. Furthermore, the risk of extrapyramidal effects with risperidone appears to be dose-dependent;[7] although similar to that for placebo overall, at doses of more than 10 mg the risk appears to approach that associated with haloperidol. In a more recent double-blind randomised study[8] the relapse rate after at least 2 years of treatment in patients with first-episode psychosis, who had initially responded to relatively small daily doses of risperidone (mean modal 3.3 mg) or haloperidol (2.9 mg), was 42% (82 of 197 patients) and 55% (111 of 203), respectively. The median time to relapse was also longer for risperidone (466 days) when compared with haloperidol (205 days). A recent review[9] concluded that there was still a lack of strong evidence for an optimal dose for risperidone but considered that doses of 4 to 6 mg daily did appear to be optimal for clinical response and adverse effects; there was also weaker evidence that 2 to 4 mg daily was of value for first episodes. In the few comparative studies with other atypical antipsychotics, risperidone has appeared to be of similar efficacy to clozapine.[10] However, another systematic review[11] concluded that such equivalence with clozapine cannot be assumed. For a systematic review of studies comparing risperidone with olanzapine, see p. 1090.3. There is insufficient evidence to indicate whether risperidone is effective for treatment-resistant or poorly responsive patients but there is some evidence that patients stabilised on risperidone may be less likely to relapse.[12] A systematic review[13] of the use of the long-acting injectable formulation of risperidone in schizophrenia considered that, although it might offer the advantage of better compliance, there was little evidence of benefit over oral use.

1. Chouinard G, *et al.* A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993; **13:** 25–40.
2. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994; **151:** 825–35.
3. Peuskens J, *et al.* Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995; **166:** 712–26.
4. Livingston MG. Risperidone. *Lancet* 1994; **343:** 457–60.
5. Musser WS, Kirisci L. Critique of the Canadian multicenter placebo-controlled study of risperidone and haloperidol. *J Clin Psychopharmacol* 1995; **15:** 226–8.
6. Hunter RH, *et al.* Risperidone versus typical antipsychotic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 30/05/05).
7. Owens DGC. Extrapyramidal side effects and tolerability of risperidone: a review. *J Clin Psychiatry* 1994; **55** (suppl 5): 29–35.
8. Schooler N, *et al.* Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 2005; **162:** 947–53.
9. Li C, *et al.* Risperidone dose for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 23/11/09).
10. Klieser E, *et al.* Randomized, double-blind, controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. *J Clin Psychopharmacol* 1995; **15** (suppl 1): 45S–51S.
11. Gilbody SM, *et al.* Risperidone versus other atypical antipsychotic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 30/05/05).
12. Csernansky JG, *et al.* A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002; **346:** 16–22.
13. Hosalli P, Davis JM. Depot risperidone for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 30/05/05).

Stuttering. Risperidone 0.5 to 2 mg daily was found to be of benefit in the management of stuttering (p. 1078.1) in a placebo-controlled study[1] involving 16 patients but there has also been a case report[2] of a patient whose stuttering returned during treatment with risperidone.

1. Maguire GA, *et al.* Risperidone for the treatment of stuttering. *J Clin Psychopharmacol* 2000; **20:** 479–82.
2. Lee H-J, *et al.* A case of risperidone-induced stuttering. *J Clin Psychopharmacol* 2001; **21:** 115–16.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) haloperidol or pimozide are commonly used but atypical antipsychotics, especially risperidone, are being increasingly tried.[1-3]

1. Bruun RD, Budman CL. Risperidone as a treatment for Tourette's syndrome. *J Clin Psychiatry* 1996; **57:** 29–31.
2. Bruggeman R, *et al.* Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry* 2001; **62:** 50–6.
3. Scahill L, *et al.* A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 2003; **60:** 1130–5.

Adverse Effects, Treatment, and Precautions

Although risperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Risperidone is reported to be less likely to cause sedation or extrapyramidal effects (see also Uses and Administration, p. 1103.2) but agitation may occur more frequently. Other common adverse effects include insomnia, anxiety, and headache. Dyspepsia, nausea and vomiting, abdominal pain, constipation, blurred vision, sexual dysfunction including priapism, urinary incontinence, rash and other allergic reactions, drowsiness, concentration difficulties, dizziness, fatigue, and rhinitis have been reported less commonly. In addition to orthostatic hypotension, hypertension has been reported infrequently. Other adverse effects with risperidone include cerebrovascular accidents, tachycardia, weight gain, oedema, and increased liver enzyme values. Risperidone may cause dose-dependent increases in prolactin levels. In rare cases, hyperglycaemia and exacerbation of pre-existing diabetes mellitus have also been reported. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes.

Other rare effects include blood dyscrasias including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia, seizures, body temperature dysregulation, hyponatraemia, neuroleptic malignant syndrome, and tardive dyskinesia.

Risperidone should be used with caution in patients with cardiovascular disease, including conditions associated with QT prolongation, or conditions predisposing to hypotension. Caution is also recommended in patients with a history of or at risk of developing cerebrovascular disease, in patients with Parkinson's disease or epilepsy, and in patients with hepatic or renal impairment.

Risperidone may affect the performance of skilled tasks such as driving.

Gradual withdrawal of risperidone is recommended because of the risk of withdrawal symptoms, including sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Breast feeding. From the study of concentrations of oral risperidone and its active metabolite, 9-hydroxyrisperidone, in the breast milk of a mother receiving 6 mg daily, it was estimated that a breast-fed infant would ingest the daily equivalent of 4.3% (as risperidone equivalents) of the weight-adjusted maternal dose.[1] Later case reports[2] of 3 women receiving oral risperidone 3 mg daily, 4 mg daily, and 1.5 mg daily estimated that a breast-fed infant would receive the daily equivalent of 2.3%, 2.8%, and 4.7%, respectively, of the weight-adjusted maternal dose. Where breast feeding occurred, in the latter 2 cases, no adverse effects were reported in the breast-fed infants; risperidone and 9-hydroxyrisperidone were not detected in the plasma of either infant.

Licensed product information states that patients receiving risperidone should not breast feed; the US information also recommends that patients should not breast feed for at least 12 weeks after intramuscular injection.

1. Hill RC, *et al.* Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol* 2000; 20: 285–6.
2. Ilett KF, *et al.* Transfer of risperidone and 9-hydroxyrisperidone into human milk. *Ann Pharmacother* 2004; 38: 273–6.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Further references.

1. Safer DJ. A comparison of risperidone-induced weight gain across the age span. *J Clin Psychopharmacol* 2004; 24: 429–36.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including risperidone, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Further references.

1. Koller EA, *et al.* Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy* 2003; 23: 735–44.
2. Ramaswamy K, *et al.* Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; 30: 589–99.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

Effects on the liver. There has been a report of 2 cases of hepatotoxicity associated with risperidone.[1] An idiosyncratic reaction to risperidone was suspected in another patient who developed hepatotoxicity after receiving only 2 doses of risperidone.[2]

1. Fuller MA, *et al.* Risperidone-associated hepatotoxicity. *J Clin Psychopharmacol* 1996; 16: 84–5.
2. Phillips EJ, *et al.* Rapid onset of risperidone-induced hepatotoxicity. *Ann Pharmacother* 1998; 32: 843.

Effects on the skin. A patient developed facial and periorbital oedema 2 weeks after her dose of risperidone reached 6 mg daily.[1] The oedema subsided when the dose was halved but recurred shortly after it was again increased to 6 mg. She had previously had a similar reaction to lithium and there was also a family history of angioedema.

1. Cooney C, Nagy A. Angio-oedema associated with risperidone. *BMJ* 1995; 311: 1204.

The elderly. After analysis of data from controlled studies there was evidence that the use of risperidone in elderly patients with **dementia** appeared to be associated with an increased risk of cerebrovascular adverse effects such as stroke and transient ischaemic attacks. In 4 studies, involving 764 such patients treated with risperidone, there were 29 cases of cerebrovascular adverse events (4 fatal) versus 7 cases (1 fatal) in 466 patients given placebo. Postmarketing data for elderly dementia patients, representing over 2.4 million patient-years of exposure, included 37 cases, of which 16 were fatal.[1]

The UK CSM[2] therefore recommended at the time that risperidone should not be used to treat behavioural problems in elderly patients with dementia (but see below). Similarly, the CSM[2] recommended that olanzapine should not be used to treat behavioural problems or dementia-related psychosis in elderly patients with dementia after analysis of placebo-controlled studies revealed a threefold increase in cerebrovascular adverse effects including stroke and a twofold increase in all-cause mortality. It was considered[2] that the risk may not be confined to use in dementia and should be considered relevant to any patient with a history of stroke or transient ischaemic attack or other risk factors for cerebrovascular disease, including hypertension, diabetes, current smoking, or atrial fibrillation.

The FDA[3] has also advised about an increased risk of death with the use of atypical antipsychotics as a group in the treatment of behavioural problems in elderly patients with dementia. Their advice was based on an unpublished analysis of 17 placebo-controlled studies involving aripiprazole, olanzapine, quetiapine, or risperidone use in elderly demented patients with behavioral disorders: the analysis found that 15 studies showed an increase in the mortality rate in the drug-treated group compared with the placebo-treated patients. A total of 5106 patients were included in these studies, and a 1.6- to 1.7-fold increase in mortality was seen; most of the deaths appeared due to cardiovascular events or infection. Another published meta-analysis[4] of placebo-controlled studies also had similar findings.

However, 3 large retrospective population-based studies in the elderly (1 involving 10 385 patients given atypicals and 1015 given classical antipsychotics,[5] another involving 17 845 given atypicals and 14 865 given classical antipsychotics,[6] and the third involving 24 359 given atypicals and 12 882 given classical antipsychotics[7]), suggested that use of atypical antipsychotics was not associated with a statistically significant increased risk of stroke compared with the classical drugs. Furthermore, UK licensed product information states that a higher incidence of mortality was seen in elderly patients with dementia who were taking risperidone and furosemide when compared with those taking either drug alone; use of risperidone with other diuretics (mainly low-dose thiazides) was not associated with such findings.

More recently, the UK CHM[8] (formerly the CSM) stated that analysis of 3 randomised studies showed a clear benefit for the short-term use of risperidone in the treatment of aggression in elderly patients with dementia. Indeed, risperidone is now licensed for such use in the UK but the balance of risks and benefits should be carefully assessed for every patient; for further details and doses see Uses and Administration, p. 1103.2.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p. 1030.2 and under Precautions of Chlorpromazine, p. 1051.1.

1. Janssen-Ortho Inc. Health Canada. Important drug safety information: Risperdal (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials (issued 11th October, 2002). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/risperdal_hpc-cps-eng.pdf (accessed 21/08/08)
2. Duff G. Atypical antipsychotic drugs and stroke: message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 9th March, 2004). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019488.pdf (accessed 21/08/08)
3. FDA. Public Health Advisory: deaths with antipsychotics in elderly patients with behavioral disturbances (issued 11th April, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm053171.htm (accessed 26/07/10)
4. Schneider LS, *et al.* Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; 294: 1934–43.
5. Herrmann N, *et al.* Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004; 161: 1113–15.
6. Gill SS, *et al.* Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ* 2005; 330: 445–8.
7. Schneeweiss S, *et al.* Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *Can Med Assoc J* 2007; 176: 627–32. Correction. *ibid.*; 1613.
8. MHRA/CHM. Antipsychotics: use in elderly people with dementia. *Drug Safety Update* 2009; 2 (8): 5–6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON041211 (accessed 03/06/09)

Extrapyramidal disorders. In reports of 3 cases of tardive dystonia associated with oral risperidone therapy,[1,2] onset ranged from 3 to 8 months after starting the drug. Dyskinesia has also been reported 5 days after the withdrawal of oral risperidone and citalopram therapy.[3] In another report,[4] three patients receiving risperidone orally developed early-onset tardive dyskinesia despite the addition of antimuscarinic therapy with biperiden or trihexyphenidyl. Extrapyramidal adverse effects have also been reported within 24 hours of intramuscular risperidone injection.[5] However, the incidence of extrapyramidal effects (p. 1049.2) is generally lower with atypical than classical antipsychotics.

1. Vercueil L, Foucher J. Risperidone-induced tardive dystonia and psychosis. *Lancet* 1999; 353: 981.
2. Krebs MO, Olie JP. Tardive dystonia induced by risperidone. *Can J Psychiatry* 1999; 44: 507–508.
3. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; 34: 269.
4. Suzuki E, *et al.* Tardive dyskinesia with risperidone and anticholinergics. *Am J Psychiatry* 2002; 159: 1948.
5. Adamou M, Hale AS. Extrapyramidal syndrome and long-acting injectable risperidone. *Am J Psychiatry* 2004; 161: 756–7.

Mania. Although it is used in the treatment of bipolar disorder, risperidone has been associated with reports of mania in both schizophrenic and bipolar patients.[1-3]

1. Dwight MM, *et al.* Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. *Lancet* 1994; 344: 554–5.
2. Zolezzi M, Badr MG. Risperidone-induced mania. *Ann Pharmacother* 1999; 33: 380–1.
3. Aubry J-M, *et al.* Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; 61: 649–55.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (p. 1050.2) has occasionally been associated with risperidone.[1-5]

1. Sharma R, *et al.* Risperidone-induced neuroleptic malignant syndrome. *Ann Pharmacother* 1996; 30: 775–8.
2. Tarsy D. Risperidone and neuroleptic malignant syndrome. *JAMA* 1996; 275: 446.
3. Reeves RR, *et al.* Neuroleptic malignant syndrome during a change from haloperidol to risperidone. *Ann Pharmacother* 2001; 35: 698–701.
4. Gerritsen AA, *et al.* Het maligne neurolepticasyndroom bij gebruik van risperidon. *Ned Tijdschr Geneeskd* 2004; 148: 1801–4.
5. Norris B, *et al.* Neuroleptic malignant syndrome with delayed onset of fever following risperidone administration. *Ann Pharmacother* 2006; 40: 2260–4.

Overdosage. A 3½-year-old child developed extrapyramidal symptoms after accidental ingestion of a single 4-mg tablet of risperidone.[1] The child was initially treated with gastric lavage, activated charcoal, and sorbitol; extrapyramidal symptoms responded to treatment with diphenhydramine and the child recovered completely. The need to monitor for and treat hypotension after overdosage with risperidone was highlighted in a report[2] of a 15-year-old girl who took 40 mg of risperidone. A 72-year-old woman receiving risperidone 6 mg daily was found unconscious, hypotensive, and hypothermic.[3] Other reported symptoms include first-degree heart block, prolonged QT interval, and respiratory arrest; she recovered after supportive treatment.

1. Cheslik TA, Erramouspe J. Extrapyramidal symptoms following accidental ingestion of risperidone in a child. *Ann Pharmacother* 1996; 30: 360–3.
2. Himstreet JE, Daya M. Hypotension and orthostasis following a risperidone overdose. *Ann Pharmacother* 1998; 32: 267.
3. Rassam S, Srinivasa R. Respiratory depression after accidental risperidone overdose. *Am J Emerg Med* 2002; 20: 570.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies risperidone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics, including risperidone, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Further references.

1. Coppola D, *et al.* Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. *Drug Safety* 2007; 30: 247–64.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by risperidone. Risperidone may also enhance the effects of antihypertensives. There may be an increased risk of QT prolongation when risperidone is given with other drugs that are known to cause this effect. Risperidone may antagonise the actions of levodopa and other dopaminergics.

Carbamazepine has been shown to decrease the antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) of risperidone and a similar effect may be seen with other enzyme inducers. Fluoxetine may increase the plasma concentrations of the antipsychotic fraction by raising the concentration of risperidone. Dose adjustment of risperidone may be necessary in such situations.

Increased mortality has been reported in elderly patients with dementia who are given risperidone and furosemide (see the Elderly, above). Caution is advised when using risperidone with furosemide or other potent diuretics.

Antiepileptics. For the effect of risperidone on *valproate*, see p. 557.3.

Antipsychotics. For a report suggesting that risperidone might increase plasma concentrations of *clozapine*, see p. 1061.3. For a report of asymptomatic QT prolongation associated with *quetiapine* in a patient also receiving risperidone, see under Overdosage of Quetiapine, p. 1102.2.

Antivirals. Dystonia and worsening of tremors were reported 1 week after adding *indinavir* and *ritonavir* to treatment with risperidone in a patient with AIDS;[1] he recovered once all 3 drugs were withdrawn and after treatment with clonazepam. An early exposure to risperidone, indinavir, and ritonavir had not resulted in any extrapyramidal adverse effects. The authors considered this to reflect the patient's relatively short exposure to risperidone at the time.

1. Kelly DV, *et al.* Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. *Ann Pharmacother* 2002; 36: 827–30.

Pharmacokinetics

Risperidone is readily absorbed after oral doses and peak plasma concentrations occur within 1 to 2 hours. It is extensively metabolised in the liver by hydroxylation to its main active metabolite, 9-hydroxyrisperidone (paliperidone, p. 1093.1); oxidative *N*-dealkylation is a minor metabolic pathway. Hydroxylation is mediated by the cytochrome P450 isoenzyme CYP2D6 and is subject to genetic polymorphism. Excretion is mainly in the urine and, to a lesser extent, in the faeces. Risperidone and 9-hydroxyrisperidone are about 90% and 77% bound to plasma proteins, respectively. Both are distributed into breast milk.

Metabolism. Although the hydroxylation of risperidone is subject to genetic polymorphism, the pharmacokinetics and effects of the active antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) have been reported to vary little between extensive and poor metabolisers.[1] A mean value of 19.5 hours has been reported for the terminal elimination half-life of the active fraction following oral doses of risperidone.[1]

1. Huang M-L, *et al.* Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. *Clin Pharmacol Ther* 1993; 54: 257–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dozic; Dropicine; Edalen; Restelea; Riatul; Risper; Risperdal; Risperin; Rispex; Roxodyn; Sequinan; ***Austral.***: Ozidal; Resdone; Rispa; Risperdal; Rixadone; ***Austria***: Aleptan; Risperdal; Rispolin†; ***Belg.***: Risperdal; ***Braz.***: Esquidon; Respidon; Ripevil; Risleptic; Risperdal; Risperix; Riss; Viverdal; Zargus; ***Canad.***: Risperdal; ***Chile***: Dagotil; Goval; Radigen; Risperdal; Spiron; ***China***: Dan Ke (单克); Jing Ping (敬平); Ke Tong (可同); Risperdal (维思通); Si Li Shu (思利舒); Suo Le (索乐); Zhuo Fei (卓菲); Zhuo Fu (卓夫); ***Cz.***: Apo-Risper; Medorisper; Ridoner; Rigenin†; Rileptid; Ripetomar†; Risepro; Rispadim†; Rispedep†; Rispedolet†; Rispedospes†; Rispemar†; Rispen; Rispera; Risperdal; Risperigamma†; Risperinin†; Risperit†; Risperstad†; Rispimed†; Rispolux; Risset†; Rorendo; Unispera†; ***Denm.***: Ripexal; Risperanne; Risperdal; Rispolept; ***Fin.***: Rispazin†; Risperdal; ***Fr.***: Risperdal; Risperdalconsta; Risperdaloro; ***Ger.***: Risocon; Rispe-Q†; Risperdal; Risperdoc†; Risperigamma; ***Gr.***: Adovia; Axelabron; Belasperdal-S; Capulton; Depolan; Depredon; Deteron; Dixine; Evitrat; Helposper; Ispredon; Lassen; Leterzin; Linipon; Lucipral; Muistin; Natibo; Nerve; Novoris; Orotral; Preridon; Psychordal; Ribex; Ridoron; Rifocus; Ripepral; Risenar; Risgal; Risidral; Rispalm; Rispefar; Rispelen; Rispen; Rispenet†; Risperascol; Risperdal; Risperom; Risperoprol; Rispersan; Rispogen; Rubrum; Sperelax; Wisperdon; Zafitral; ***Hong Kong***: Rileptid; Risperdal; Risperigamma; ***Hung.***: Hunperdal; Perdox; Rileptid; Ripedon; Rispe; Risperdal; Rispolux; Rispons; Ronkal†; Rosipin; Torendo; Ziperid; ***India***: Cinris; Genrest; Respidon; Risnia; Risperdal; Rispid; Rozidal; ***Indon.***: Neripros; Nodiril; Persidal; Risperdal; Rizodal; Zofredal; ***Irl.***: Perdamel; Resdal†; Rispal; Rispatal; Risperdal; Risperger; Rispeva; Rispone; ***Israel***: Rispefar; Risperdal; Risperidex; Rispond; Speridone; ***Ital.***: Belivon; Risperdal; ***Jpn***: Risperdal; ***Malaysia***: Risperdal; Rozidal; ***Mex.***: Limbik; Reskizol; Risperdal; Rispolux; Silderec; Upmotev; ***Neth.***: Belivon†; Rispenon†; Risperdal; Rispimed†; Rispimedica†; Torendo†; ***Norw.***: Risperdal; Rispolept; ***NZ***: Ridal; Risperdal; Risperon; ***Philipp.***: Aspidon; Renuvie; Rileptid; Risdin; Rispedin; Risperdal; Rispond; ***Pol.***: Apo-Risperid; Disaperid; Doresol; Galperinon; Lioxam†; Mepharis†; Nodir; Orizon; Ranperidon; Rispen; Risperatio†; Risperiwin†; Risperon; Rispofren†; Rispolept; Rispolux; Risset; Ryspolit; Speridan; Torendo; Ziperid; ***Port.***: Itraxel; Lergitec; Lotin; Neclav; Perdin; Ripax; Risperdal; Smissen†; Zoridal; ***Rus.***: Leptinorm (Лептинорм); Neipllept (Нейплепт); Ridonex (Ридонекс); Rileptid (Рилептид); Risdonal (Рисдонал); Rispaksole (Риспаксол); Rispen (Риспен); Rispolept (Рисполепт); Rispolux (Риспомокс); Risset (Риссет); Sizodon (Сизодон); Speridan (Спередан); Torendo (Торендо); ***S.Afr.***: Perizal; Rispacor; Rispacor; Risperdal; Risperlet; Risponz; Rutra; Schizorol; Zoxadon; ***Singapore***: Ridal; Risperdal; ***Spain***: Arketin; Atornil†; Calmapride; Diaforin; Risfarmal†; Rispemylan; Risperdal; ***Swed.***: Risperdal; ***Switz.***: Risperdal; ***Thai.***: Neuris; Risperdal; ***Turk.***: Nodirep; Perilife; Restela; Ricus; Ricus; Ripesil; Risperdal; Rixol; Rixper; ***UK***: Risperdal; ***Ukr.***: Neirispin (Нейриспин); Ridonex (Ридонекс); Rileptid (Рилептид); Rispaxol (Риспаксол); Risperon (Рисперон); Rispond (Риспонд); Risset (Риссет); ***USA***: Risperdal; ***Venez.***: Ridal; Risperdal; Risperid.

Multi-ingredient Preparations. ***India***: Cinris Forte; Don Forte; Don Plus; Don-LS; Etores-TR; Genrest Plus; Genrest-LS.

Pharmacopoeial Preparations

USP 36: Risperidone Oral Solution; Risperidone Orally Disintegrating Tablets; Risperidone Tablets.

Romifidine *(BAN, rINN)*

Romifidiini; Romifidin; Romifidina; Romifidinum; STH-2130; Ромифидин.

2-Bromo-6-fluoro-*N*-(1-imidazolin-2-yl)aniline.

$C_9H_8BrFN_3$=258.1

CAS — 65896-16-4.

ATC Vet — QN05CM93.

UNII — 876351L05K.

Profile

Romifidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties and is used in veterinary medicine.

Secbutabarbital *(rINN)*

Butabarbital; Butabarbitone; Secbutabarbitalum; Secbutobarbital (BAN); Secbutobarbitone; Секбутабарбитал.

5-sec-Butyl-5-ethylbarbituric acid.

$C_{10}H_{16}N_2O_3$=212.2

CAS — 125-40-6.

UNII — P0078O25A9.

NOTE. Care should be taken to avoid confusion between barbiturates with similar names: Butabarbital, a synonym for Secbutabarbital, should be distinguished from Butobarbital (p. 1044.1), and Secbutabarbital should be distinguished from Secobarbital (below).

Pharmacopoeias. In *US*.

USP 36: (Butabarbital). A white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol, in chloroform, in ether, and in aqueous solutions of alkali hydroxides and carbonates. Store in airtight containers.

Secbutabarbital Sodium *(rINNM)*

Butabarbital Sodium; Natrii Secbutabarbitalum; Secbutabarbital sódico; Secbutabarbital Sodique; Secbutobarbital Sodium (BANM); Secbutobarbitone Sodium; Secumalnatrium; Sodium Butabarbital; Натрий Секбутабарбитал.

Sodium 5-sec-butyl-5-ethylbarbiturate.

$C_{10}H_{15}N_2NaO_3$=234.2

CAS — 143-81-7.

UNII — 9WTD50I918.

Pharmacopoeias. In *US*.

USP 36: (Butabarbital Sodium). A white powder. Soluble 1 in 2 of water, 1 in 7 of alcohol, and 1 in 7000 of chloroform; practically insoluble in absolute ether. pH of a 10% solution in water is between 10.0 and 11.2. Store in airtight containers.

Profile

Secbutabarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.2). It has been used as a hypnotic and sedative although barbiturates are no longer considered appropriate for such purposes. For the short-term management of insomnia (p. 1033.2) it was usually given as the sodium salt in oral doses of 50 to 100 mg at night; as a sedative 15 to 30 mg has been given 3 or 4 times daily. Secbutabarbital base has also been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Butisol.

Multi-ingredient Preparations. ***USA***: Butibel; Phenazopyridine Plus; Pyrelle HB†; Urelief Plus; ***Venez.***: Butropina; Eumidral.

Pharmacopoeial Preparations

USP 36: Butabarbital Sodium Elixir; Butabarbital Sodium Tablets.

Secobarbital *(rINN)*

Meballymal; Quinalbarbitone; Sécobarbital; Secobarbitalum; Secobarbitone; Sekobarbitaali; Секобарбитал.

5-Allyl-5-(1-methylbutyl)barbituric acid.

$C_{12}H_{18}N_2O_3$=238.3

CAS — 76-73-3.

ATC — N05CA06.

ATC Vet — QN05CA06; QN51AA02.

UNII — 1P7H87IN7S.

NOTE. Care should be taken to avoid confusion between barbiturates with similar names: Secobarbital should be distinguished from Secbutabarbital (above).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of secobarbital:

F-40s; Marshmallow reds; M&Ms; Mexican reds; Pink ladies; Pink lady; Pinks; RDs; Red birds; Red bullets; Red devil; Red devils; Red dolls; Red lillies; Reds; Seccies; Seccy; Seco; Seggy.

Pharmacopoeias. In *US*.

USP 36: (Secobarbital). A white amorphous or crystalline odourless powder. Very slighrly soluble in water; freely soluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates; soluble in chloroform; soluble in 8.5 of 0.5N sodium hydroxide. A saturated solution in water has a pH of about 5.6. Store in airtight containers.

Secobarbital Sodium *(BAN, rINNM)*

Meballymalnatrium; Natrii Secobarbitalum; Quinalbarbitone Sodium; Secobarbital sódico; Sécobarbital Sodique; Secobarbitalum Natricum; Secobarbitone Sodium; Натрий Секобарбитал.

Sodium 5-allyl-5-(1-methylbutyl)barbiturate.

$C_{12}H_{17}N_2NaO_3$=260.3

CAS — 309-43-3.

ATC — N05CA06.

ATC Vet — QN05CA06.

UNII — XBP604F6UM.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Secobarbital Sodium). A white odourless hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in ether. pH of a 10% solution in water is between 9.7 and 10.5. Solutions decompose on standing, heat accelerating the decomposition. Store in airtight containers.

Incompatibility. Secobarbital may be precipitated from preparations containing secobarbital sodium depending on the concentration and pH. Secobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Uses and Administration

Secobarbital is a barbiturate with general properties similar to those of amobarbital (p. 1037.3). It has been used as a hypnotic and sedative but can no longer be recommended because of its adverse effects and risk of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p. 1033.2) in patients already taking it. It was usually given in an oral dose of 100 mg of the sodium salt at night. For premedication in anaesthetic procedures (p. 1899.1) the sodium salt has been given orally or by intramuscular or intravenous injection although barbiturates for preoperative sedation have generally been replaced by other drugs.

Dependence and Withdrawal

As for Amobarbital, p. 1038.1.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p. 1038.1.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving secobarbital, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding. However, for the view that barbiturates should not be used in women who are breast feeding, see under Amobarbital, p. 1038.2.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Industrial exposure. Exposure to secobarbital sodium among 6 workers in the pharmaceutical industry resulted in absorption of substantial amounts of the drug, with

blood concentrations approaching those expected after a therapeutic dose.[1] There continued to be evidence of absorption, despite protective masks to reduce inhalation, and it appeared that substantial absorption was taking place through the skin.

1. Baxter PJ, *et al.* Exposure to quinalbarbitone sodium in pharmaceutical workers. *BMJ* 1986; **292:** 660–1.

Interactions

As for Amobarbital, p. 1038.2.

Pharmacokinetics

Secobarbital is well absorbed from the gastrointestinal tract after oral doses and is reported to be about 46 to 70% bound to plasma proteins. The mean elimination half-life is reported to be 28 hours, with a range of 15 to 40 hours. It is metabolised in the liver, mainly by hydroxylation, and excreted in the urine as metabolites and a small amount of unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Ional; *UK*: Seconal; *USA*: Seconal.

Multi-ingredient Preparations. *UK*: Tuinal; *USA*: Tuinal.

Pharmacopoeial Preparations
USP 36: Secobarbital Sodium and Amobarbital Sodium Capsules; Secobarbital Sodium Capsules; Secobarbital Sodium for Injection; Secobarbital Sodium Injection.

Sertindole *(BAN, USAN, rINN)*

Lu-23-174; Sertindol; Sertindoli; Sertindolum; Сертиндол.
1-(2-{4-[5-Chloro-1-(*p*-fluorophenyl)indol-3-yl]piperidino}ethyl)-2-imidazolidinone.
$C_{24}H_{26}ClFN_4O$=440.9
CAS — 106516-24-9.
ATC — N05AE03.
ATC Vet — QN05AE03.
UNII — GVV4Z879SP.

Uses and Administration

Sertindole is an atypical antipsychotic that is an antagonist at central dopamine (D_2), serotonin (5-HT_2), and adrenergic (α_1) receptors. It is used in the treatment of schizophrenia (p. 1031.3) in patients who are unable to tolerate at least one other antipsychotic. In addition, sertindole should only be prescribed to patients enrolled in clinical studies to ensure adequate monitoring, especially regular ECG measurements (see Adverse Effects, below).

Sertindole is given in an initial oral dose of 4 mg once daily, increased gradually in steps of 4 mg every 4 or 5 days to a usual maintenance dose of 12 to 20 mg once daily. The maximum dose is 24 mg daily. Slower dose titration and lower maintenance doses are advisable for the elderly and patients with mild to moderate hepatic impairment.

If therapy is interrupted for 1 week or more, the dose of sertindole should be re-titrated. An ECG should also be undertaken before re-starting sertindole.

References.
1. Lewis R. *et al.* Sertindole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/05/06).

Adverse Effects, Treatment, and Precautions

Although sertindole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Sertindole is associated with a low incidence of extrapyramidal adverse effects and does not appear to cause sedation. Prolactin elevation may be less frequent. The most common adverse effects with sertindole are peripheral oedema, rhinitis, dyspnoea, sexual dysfunction, dizziness, dry mouth, orthostatic hypotension, weight gain, and paraesthesia. Hyperglycaemia, convulsions, and tardive dyskinesia are uncommon.

Marketing of sertindole has been restricted because of cardiac arrhythmias and sudden cardiac deaths associated with its use (see below). Since sertindole has been associated with prolongation of the QT interval, usually during the first 3 to 6 weeks of treatment, it is recommended that patients should have an ECG before the start of therapy and periodically during treatment. Patients with pre-existing prolongation of the QT interval or a family history of congenital QT prolongation should not be given sertindole and sertindole should be stopped if such prolongation occurs during treatment. In addition, sertindole is contra-indicated in patients with a history of cardiovascular disease, heart failure, cardiac hypertrophy, arrhythmias, or bradycardia. Certain medications may also increase the risk (see Interactions, below).

Sertindole should not be given to patients with uncorrected hypokalaemia or hypomagnesaemia. Baseline serum potassium and magnesium screening should be performed before starting sertindole therapy in patients who are at risk of significant electrolyte disturbances. Serum potassium should be monitored in patients with electrolyte disturbances, vomiting or diarrhoea, or receiving diuretics during sertindole treatment. It is also recommended that blood pressure should be monitored during dose titration and in early maintenance therapy.

Sertindole is contra-indicated in patients with severe hepatic impairment. It should be used with caution in the elderly and in patients with Parkinson's disease, mild to moderate hepatic impairment, or a history of seizures.

Sertindole may affect the performance of skilled tasks including driving.

Gradual withdrawal of sertindole is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. Prolongation of the QT interval is said by the manufacturer to be common in patients given sertindole, with the effect being greater at the upper end of the dose range. In addition, the QT interval is prolonged to a greater extent than that seen with some other antipsychotics. QT interval prolongation is a known risk factor for the development of serious arrhythmias such as torsade de pointes although such arrhythmias are uncommon with sertindole.

In evidence presented to the FDA it was reported that as of 1st June 1996 there had been 27 deaths, 16 due to adverse cardiac events, among the 2194 patients given sertindole in clinical studies.[1] By the end of November 1998, the UK CSM was aware of 36 suspected adverse drug reactions with a fatal outcome, 9 of which originated in the UK.[2] There had also been 13 reports of serious but non-fatal cardiac arrhythmias in the UK. Although not all the fatalities were related to sudden cardiac events, at the time the CSM considered that, given the number of serious arrhythmias and sudden cardiac deaths, the risk-benefit ratio of sertindole was no longer favourable. The drug was withdrawn from the market in the UK and subsequently in some other countries, although it remained available on a named-patient basis. However, in 2001, the issue was re-evaluated by the CSM and the European advisory body, the Committee on Proprietary Medicinal Products, and it was recommended that sertindole could be reintroduced in Europe under certain restrictions.[3] Initially sertindole should only be prescribed to patients enrolled in clinical studies to ensure that they are carefully selected and monitored. In the UK, sertindole was remarketed in September 2002.

The risk of sudden unexpected deaths associated with antipsychotic use in general is discussed under Adverse Effects of Chlorpromazine, p. 1047.3.

1. Barnett AA. Safety concerns over antipsychotic drug, sertindole. *Lancet* 1996; **348:** 256.
2. CSM/MCA. Suspension of availability of sertindole (Serdolect). *Current Problems* 1999; **25:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023236&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
3. CSM/MCA. Restricted re-introduction of the atypical antipsychotic sertindole (Serdolect) (issued 10th September, 2002). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019523 (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p. 1061.2.

Interactions

The risk of arrhythmias with sertindole may be increased by other drugs that prolong the QT interval and use together should be avoided. Sertindole should be given with caution with drugs that produce electrolyte disturbances; monitoring of serum potassium is recommended if given with potassium-depleting diuretics.

Sertindole may antagonise the effects of dopaminergics.

Sertindole is extensively metabolised by the cytochrome P450 isoenzymes of the group CYP3A and by CYP2D6. The use of potent inhibitors of CYP3A such as indinavir, itraconazole, and ketoconazole with sertindole is contra-indicated. Minor increases in sertindole plasma concentrations have been noted in patients given macrolide antibacterials or calcium-channel blockers which also inhibit CYP3A; the use of these CYP3A4 inhibitors with sertindole is not recommended despite the small increase. Fluoxetine and paroxetine, potent inhibitors of CYP2D6, have increased plasma concentrations of sertindole by a factor of 2 to 3 and lower maintenance doses of sertindole may be required. In contrast, enzyme inducers such as rifampicin, carbamazepine, phenytoin, and phenobarbital may decrease sertindole plasma levels by a factor of 2 to 3; in such cases, higher doses of sertindole may be required.

Pharmacokinetics

Sertindole is slowly absorbed and peak concentrations occur about 10 hours after oral doses. It is about 99.5% bound to plasma proteins and readily crosses the placenta. Sertindole is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A. There is moderate interindividual variation in the pharmacokinetics of sertindole due to polymorphism in the isoenzyme CYP2D6. Poor metabolisers, deficient in this isoenzyme, may have plasma concentrations of sertindole 2 to 3 times higher than other patients. The two major metabolites, dehydrosertindole and norsertindole, appear to be inactive. Sertindole and its metabolites are excreted slowly, mainly in the faeces with a minor amount appearing in the urine. The mean terminal half-life is about 3 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Serdolect; ***Austral.***: Serdolect; ***Austria***: Serdolect; ***Belg.***: Serdolect; ***Cz.***: Serdolect; ***Denm.***: Serdolect; ***Fin.***: Serdolect; ***Ger.***: Serdolect; ***Gr.***: Serdolect; ***Hung.***: Serdolect; ***Irl.***: Serdolect; ***Israel***: Serdolect; ***Malaysia***: Serdolect; ***Mex.***: Serlect; ***Neth.***: Serdolect; ***Norw.***: Serdolect; ***NZ***: Serdolect; ***Philipp.***: Serdolect; ***Pol.***: Serdolect; ***Port.***: Serdolect; ***Rus.***: Serdolect (Сердолект); ***Spain***: Serdolect; ***Swed.***: Serdolect; ***Switz.***: Serdolect; ***Turk.***: Serdolect; ***UK***: Serdolect†; ***Ukr.***: Serdolect (Сердолект).

Spiperone *(BAN, USAN, rINN)*

Espiperona; R-5147; Spipérone; Spiperonum; Spiroperidol; Спиперон.
8-[3-(4-Fluorobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.
$C_{23}H_{26}FN_3O_2$=395.5
CAS — 749-02-0.
UNII — 4X6E73CJ0Q.

Profile

Spiperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It has been given orally in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Spiropitan.

Sulpiride *(BAN, USAN, rINN)*

Sulpirid; Sulpirida; Sulpiridas; Sulpiridi; Sulpiridum; Sülprid; Szulpirid; Сульпирид.
N-(1-Ethylpyrrolidin-2-ylmethyl)-2-methoxy-5-sulphamoylbenzamide.
$C_{15}H_{23}N_3O_4S$=341.4
CAS — 15676-16-1 (sulpiride).
ATC — N05AL01.
ATC Vet — QN05AL01.
UNII — 7MNE9M8287.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Sulpiride). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in

The symbol † denotes a preparation no longer actively marketed

methyl alcohol. It dissolves in dilute solutions of mineral acids and in alkali hydroxides.

Levosulpiride *(rINN)*

Levosulpirida; Lévosulpiride; Levosulpiridum; Levosulpride; L-Sulpiride; Левосульпирид.

$C_{15}H_{23}N_3O_4S$=341.4.

CAS — 23672-07-3.

ATC — N05AL07.

ATC Vet — QN05AL07.

UNII — JTG7R315LK.

Uses and Administration

Sulpiride is a substituted benzamide antipsychotic that is reported to be a selective antagonist of central dopamine (D_2, D_3, and D_4) receptors. It is also claimed to have mood elevating properties.

Sulpiride is mainly used in the treatment of psychoses such as schizophrenia (below). It has also been given in the management of Tourette's syndrome (below), anxiety disorders, depression, vertigo, and benign peptic ulceration (see Gastrointestinal Disorders, below). Levosulpiride, the L-isomer of sulpiride, has been used similarly to sulpiride.

In the treatment of **schizophrenia** in adults and children aged 14 years and over, initial oral doses of 200 to 400 mg of sulpiride are given twice daily, increased if necessary up to a maximum of 1.2 g twice daily in patients with mainly positive symptoms or up to a total of 800 mg daily in patients with mainly negative symptoms. Patients with mixed positive and negative symptoms, with neither predominating, are given usual doses of 400 to 600 mg twice daily. Lower initial doses have been recommended in elderly patients, subsequently adjusted as required.

Sulpiride is also given in some countries by intramuscular injection, in usual doses ranging from 200 to 800 mg daily.

Dosage adjustment is advised in patients with renal impairment (see below).

Administration in children. For details of doses in the treatment of Tourette's syndrome in children, see below. For details of adolescent doses in the treatment of schizophrenia, see above.

Administration in renal impairment. A single intravenous dose of sulpiride 100 mg was given to 6 healthy subjects with normal renal function (creatinine clearance greater than 90 mL/minute) and to 3 groups of 6 patients each with creatinine clearances (CC) in the ranges of 30 to 60, 10 to 30, and less than 10 mL/minute.[1] There was a progressive diminution in the rate of elimination and an increase in half-life with decreasing renal function. The mean plasma elimination half-lives were 5.90, 11.02, 19.27, and 25.96 hours in the 4 groups, respectively.

Licensed product information suggests that dosage reduction or longer dosage interval may be required in patients with renal impairment, but gives no specific advice on how to do this.

1. Bressolle F, *et al.* Pharmacokinetics of sulpiride after intravenous administration in patients with impaired renal function. *Clin Pharmacokinet* 1989; 17: 367–73.

Chorea. Antipsychotics have some action against choreiform movements (p. 1029.3) as well as being of use to control the behavioural disturbances of Huntington's chorea. Although sulpiride was found to have produced an overall reduction in abnormal movements in 11 patients with Huntington's chorea when compared with placebo in a double-blind study[1] there was generally no accompanying functional improvement and patients with mild disease tended to worsen when taking sulpiride.

1. Quinn N, Marsden CD. A double blind trial of sulpiride in Huntington's disease and tardive dyskinesia. *J Neurol Neurosurg Psychiatry* 1984; 47: 844–7.

Gastrointestinal disorders. Although sulpiride is used in some countries as an adjunct in the treatment of peptic ulcer disease (p. 1816.2) it is not among the more usual drugs used for this indication. Efficacy has also been claimed for sulpiride or levosulpiride in a variety of other gastrointestinal disorders, including irritable bowel disease (p. 1813.3), decreased gastrointestinal motility (p. 1808.2), and nausea and vomiting (p. 1814.3), but again they are not among the drugs usually considered for use in these conditions.

Lactation induction. Drug therapy has been used occasionally to stimulate lactation in breast-feeding mothers, although good maternal education and support in techniques that promote physiological lactation remain the most important methods. Dopamine antagonists such as sulpiride can produce modest increases in breast milk production[1-3] although metoclopramide has been more widely used (see p. 2130.1). However, there is concern about the adverse effects of these drugs. As sulpiride appears in breast milk and may be associated with adverse effects in the infant it has been recommended that it should not be used to enhance milk production.[4,5]

1. Aono T, *et al.* Effect of sulpiride on poor puerperal lactation. *Am J Obstet Gynecol* 1982; 143: 927–32.
2. Ylikorkala O, *et al.* Sulpiride improves inadequate lactation. *BMJ* 1982; 285: 249–51.
3. Ylikorkala O, *et al.* Treatment of inadequate lactation with oral sulpiride and buccal oxytocin. *Obstet Gynecol* 1984; 63: 57–60.
4. Pons G, *et al.* Excretion of psychoactive drugs into breast milk: pharmacokinetic principles and recommendations. *Clin Pharmacokinet* 1994; 27: 270–89.
5. Lasich AJ. Sulpiride and breastfeeding. *S Afr Med J* 2005; 95: 624–6.

Schizophrenia. A systematic review[1] of the use of sulpiride for schizophrenia (p. 1031.3) or serious mental illness concluded that while sulpiride might be as effective as the classical antipsychotics for schizophrenia and appeared to produce few adverse effects, evidence of its value for treating negative symptoms was lacking. Comparisons with the atypical antipsychotic drugs were also lacking.

1. Soares B, *et al.* Sulpiride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 21/08/08).

Tourette's syndrome. When drug treatment is needed for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1) dopamine antagonists such as the antipsychotics haloperidol or pimozide are most commonly used but sulpiride has also been tried.[1] Although unlicensed in the UK for the treatment of Tourette's syndrome, the *BNFC* has suggested that oral doses of sulpiride 50 to 400 mg twice daily may be given to children aged from 2 to 12 years, and 100 to 400 mg twice daily to adolescents aged from 12 to 18 years.

1. Robertson MM, *et al.* Management of Gilles de la Tourette syndrome using sulpiride. *Clin Neuropharmacol* 1990; 13: 229–35.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Sleep disturbances, overstimulation, and agitation may occur. Extrapyramidal effects appear to be as frequent as with chlorpromazine but have usually been mild. It has been suggested that sulpiride is less likely to cause tardive dyskinesia but good evidence of any important difference is lacking. Sulpiride is less likely to cause sedation than chlorpromazine and antimuscarinic effects are minimal. Cardiovascular effects such as hypotension are generally rare although they may occur with overdosage.

Sulpiride should be given with care to manic or hypomanic patients in whom it may exacerbate symptoms.

Breast feeding. Sulpiride may be distributed into breast milk and the *BNF* recommends that its use should be avoided in mothers wishing to breast feed.

On the fifth day after starting D-sulpiride, DL-sulpiride, or L-sulpiride in a dose of 50 mg twice daily, mean concentrations of sulpiride in breast milk from 45 women were 840, 850, and 810 nanograms/mL respectively.[1]

1. Polatti F. Sulpiride isomers and milk secretion in puerperium. *Clin Exp Obstet Gynecol* 1982; 9: 144–7.

Effects on the cardiovascular system. Sulpiride 100 mg orally caused an attack of hypertension in 6 of 26 hypertensive patients; in 4 it induced a rise in urinary excretion of vanillylmandelic acid and catecholamines.[1] A transient rise in blood pressure and catecholamines after sulpiride occurred in 3 patients who were found to have a phaeochromocytoma; another patient probably had a phaeochromocytoma. The means by which sulpiride provoked hypertension were not known but appeared to be due to a noradrenergic effect. Sulpiride should be avoided during the treatment of phaeochromocytoma, and prescribed with great care in hypertensive patients.

1. Corvol P, *et al.* Poussées hypertensives déclenchées par le sulpiride. *Sem Hop Paris* 1974; 50: 1265–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulpiride as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] However UK licensed product information contra-indicates sulpiride use in porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Renal impairment. For the precautions to be observed in patients with impaired renal function, see under Uses and Administration, above.

Interactions

As for Chlorpromazine, p. 1051.3

Gastrointestinal drugs. Giving sulpiride with therapeutic doses of *sucralfate* or an *antacid* containing aluminium and magnesium hydroxides to 6 healthy subjects reduced the mean oral bioavailability of sulpiride by 40 and 32%, respectively.[1] When sulpiride was given 2 hours after the antacid or sucralfate (each in 2 subjects), bioavailability was reduced by about 25%. This interaction was expected to be clinically significant, and it was recommended that sulpiride should be given before, rather than with or after, sucralfate or antacids.

1. Gouda MW, *et al.* Effect of sucralfate and antacids on the bioavailability of sulpiride in humans. *Int J Pharmaceutics* 1984; 22: 257–63.

Pharmacokinetics

Sulpiride is slowly absorbed from the gastrointestinal tract; peak plasma concentrations are attained 3 to 6 hours after ingestion. Bioavailability is low and subject to interindividual variation. It is rapidly distributed to the tissues but at passage across the blood-brain barrier is poor. Sulpiride is about 40% bound to plasma proteins and is reported to have a plasma half-life of about 8 to 9 hours. It is excreted in the urine and faeces, mainly as unchanged drug. Sulpiride is distributed into breast milk.

References.

1. Wiesel F-A, *et al.* The pharmacokinetics of intravenous and oral sulpiride in healthy human subjects. *Eur J Clin Pharmacol* 1980; 17: 385–91.
2. Bressolle F, *et al.* Sulpiride pharmacokinetics in humans after intramuscular administration at three dose levels. *J Pharm Sci* 1984; 73: 1128–36.
3. Bressolle F, *et al.* Absolute bioavailability, rate of absorption, and dose proportionality of sulpiride in humans. *J Pharm Sci* 1992; 81: 26–32.
4. Mauri MC, *et al.* L-sulpiride in young and elderly negative schizophrenics: clinical and pharmacokinetic variables. *Prog Neuropsychopharmacol Biol Psychiatry* 1994; 18: 355–6.
5. Muller MJ, *et al.* Serum levels of sulpiride enantiomers after oral treatment with racemic sulpiride in psychiatric patients: a pilot study. *Pharmacopsychiatry* 2001; 34: 27–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dislep; Vipral; *Austria*: Dogmatil; Meresa†; Meresasul; *Belg.*: Docsulpirit†; Dogmatil; Levopraid; *Braz.*: Dogmatil; Equilid; *Chile*: Aplacid; Dislep; Endacine; Istefral; Sanblex; Sedusen; Sulpilan; Sulpivol; *Cz.*: Dogmatil; Prosulpin; Sulpirol; *Denm.*: Dogmatil; Dolmatil; *Fin.*: Suprium; *Fr.*: Dogmatil; Synedil; *Ger.*: Arminol†; Dogmatil†; Meresa; Meresasul; neogama†; Sulpivert; Vertigo-Meresa; vertigo-neogama; *Gr.*: Calmoflorine; Darleton; Desmenat; Dogmatyl; Eclorion; Esalfon; Fardalan; Fidelan; Mariastel; Nonestón; Nufarol; Nylipark; Omaha; Omiryl; Ozoderpin; Restful; Silavidon; Stamonevrol; Valirem; Zymocomb; *Hong Kong*: Dogmatil; Spanomid†; *Hung.*: Depral; *India*: Lesuride; Levoride; Nexipride; *Indon.*: Dogmatil; *Irl.*: Dolmatil; *Israel*: Modal; *Ital.*: Championyl; Dobren; Equilid; Levobren; Levopraid; *Jpn*: Dogmatyl; *Malaysia*: Dogmatil; Sulpin; *Mex.*: Dislep; Ekilid; Pontiride; Rimastine; *Neth.*: Dogmatil; *Philipp.*: Dogmatil†; *Port.*: Dogmatil; *Rus.*: Betamax (Бетамакс); Eglek (Эглек); Eglonil (Эглонил); Prosulpin (Просульпин); *S.Afr.*: Eglonyl; Espiride; *Singapore*: Devodil; Dogmatil; Sulris; *Spain*: Digton†; Dogmatil Guastil; Lebopride†; Levogastrol; Pausedal; Psicocen; Tepavil; *Switz.*: Dogmatil; *Turk.*: Dogmatil; Meresa; Sulpir; Zeprid; *UK*: Dolmatil; Sulpor; *Ukr.*: Betamax (Бетамакс); Eglonil (Эглонил); *Venez.*: Dislep.

Multi-ingredient Preparations. *Arg.*: Alplax Digest; Tranquina Soma; Tranxilium Digest; Vegestabil; *Braz.*: Bromopirin; Sulpan; *Mex.*: Neupax Duo-S; Numencial; *Spain*: Ansium; Tepazepan.

Pharmacopoeial Preparations

BP 2014: Sulpiride Tablets.

Sultopride Hydrochloride *(rINNM)*

Hidrocloruro de sultoprida; LIN-1418; Sultoprida, hidrocloruro de; Sultopride, Chlorhydrate de; Sultopridi Hydrochloridum; Сультоприда гидрохлорид.

N-(1-Ethylpyrrolidin-2-ylmethyl)-5-ethylsulphonyl-2-methoxybenzamide hydrochloride.

$C_{17}H_{26}N_2O_4S,HCl$=390.9

CAS — 53583-79-2 (sultopride); 23694-17-9 (sultopride hydrochloride).

ATC — N05AL02.

ATC Vet — QN05AL02.

Profile

Sultopride is a substituted benzamide with general properties similar to those of sulpiride (p. 1107.3). It has been used in psychoses such as schizophrenia (p. 1031.3). It has also been used in the emergency management of agitation in psychotic or aggressive patients.

Ventricular arrhythmias, including torsade de pointes, have been reported. It has been recommended that sultopride should not be used in patients with bradycardia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Barnetil; *Rus.*: Topral (Топрал).

Tandospirone Citrate *(BANM, USAN, rINNM)*

Citrato de tandospirona; Metanopirone Citrate; SM-3997 (tandospirone or tandospirone citrate); Tandospirona, citrato de; Tandospirone, Citrate de; Tandospironi Citras; Тандоспирона Цитрат.

(1R*,2S*,3R*,4S*)-*N*-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-2,3-norbornanedicarboximide citrate.

$C_{21}H_{29}N_5O_2,C_6H_8O_7$=575.6

CAS — 87760-53-0 (tandospirone); 112457-95-1 (tandospirone citrate).

UNII — 0R8E9BWM4J.

Profile

Tandospirone, a partial agonist at serotonin (5-HT) receptors of the 5-HT_{1A} subtype, is an anxiolytic structurally related to buspirone (p. 1042.1). It also has antidepressant actions. Tandospirone citrate is given in usual oral doses of 30 mg daily in 3 divided doses up to a maximum of 60 mg daily.

References.

1. Sumiyoshi T, *et al.* The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. *Biol Psychiatry* 2001; 49: 861–8.
2. Yamada K, *et al.* Clinical efficacy of tandospirone augmentation in patients with major depressive disorder: a randomized controlled trial. *Psychiatry Clin Neurosci* 2003; 57: 183–7.
3. Takei A, *et al.* Treatment of cerebellar ataxia with 5-HT1A agonist. *Cerebellum* 2005; 4: 211–15.
4. Miwa H, *et al.* Efficacy of the 5-HT1A agonist tandospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. *Am J Gastroenterol* 2009; 104: 2779–87.

Bruxism. Tandospirone has been tried in the management of bruxism; for further details, see under Buspirone, p. 1042.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Lv Kang (律康); Sediel (希德); *Jpn*: Sediel.

Tasimelteon *(USAN, rINN)*

BMS-214778; Tasimelteón; Tasimeltéon; Tasimelteonum; VEC-162; Тасимелтеон.

N-[[(1*R*,2*R*)-2-(2,3-Dihydro-1-benzofuran-4-yl)cyclopropyl]methyl]propanamide.

$C_{15}H_{19}NO_2$=245.3

CAS — 609799-22-6.

UNII — SHS4PU8009.

Profile

Tasimelteon is a melatonin receptor agonist that is being investigated for the treatment of transient insomnia associated with circadian rhythm disturbances such as those caused by shift work or jet lag.

References.

1. Rajaratnam SMW, *et al.* Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 2009; 373: 482–91.
2. Hardeland R. Tasimelteon, a melatonin agonist for the treatment of insomnia and circadian rhythm sleep disorders. *Curr Opin Investig Drugs* 2009; 10: 691–701.

Temazepam *(BAN, USAN, rINN)*

ER-115; 3-Hydroxydiazepam; K-3917; Ro-5-5345; Tematsepaami; Temazepám; Témazépam; Temazepamas; Temazepamum; Wy-3917; Темазепам.

7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-1,4-benzodiazepin-2-one.

$C_{16}H_{13}ClN_2O_2$=300.7

CAS — 846-50-4.

ATC — N05CD07.

ATC Vet — QN05CD07.

UNII — CHB1QD2QSS.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of temazepam:

Beans; Egg; Eggs; Jellies; Jelly babies; Knockout Pills; Mazzies; Oranges; Rugby Balls; Temazies; Temmies; Terms; Wobbly Jellies; Yellow eggs.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Temazepam). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Temazepam). A white or nearly white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from light.

Uses and Administration

Temazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (p. 1033.2) and for premedication before surgical or investigative procedures (see Anaesthesia, p. 1899.1).

A usual oral dose for insomnia is 10 to 20 mg at night; exceptionally, doses up to 40 mg may be required. For premedication the usual oral dose is 20 to 40 mg given half to one hour beforehand.

Temazepam should be given in reduced dosage to elderly or debilitated patients; half of the usual adult dose, or less, may be sufficient (see also Administration in the Elderly, below).

For details of doses in children, see Administration in Children, below.

Administration. For reference to the various formulations of oral temazepam that have been used, see Abuse under Adverse Effects, Treatment, and Precautions, below.

Administration in children. Temazepam may be given to children for premedication before surgical or investigative procedures. In the UK, licensed product information recommends a dose of 1 mg/kg as an oral solution 1 hour beforehand; the *BNFC* only recommends use in older children, and suggests that those aged 12 to 18 years may be given an oral dose of 10 to 20 mg.

Administration in the elderly. In a small study[1] a 7.5-mg dose of temazepam was found to be adequate for the short-term management of insomnia in elderly patients.

1. Vgontzas AN, *et al.* Temazepam 7.5 mg: effects on sleep in elderly insomniacs. *Eur J Clin Pharmacol* 1994; 46: 209–13.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 10 mg of temazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Abuse. Liquid-filled temazepam *capsules* were widely abused on the illicit drugs market, the liquid gel lending itself to intravenous injection.[1] This formulation was, therefore, replaced in some countries by tablets or by semi-solid gel-filled capsules, which were intended to be difficult to inject even after heating or diluting the gel in various solvents.[2] In spite of this there is evidence of intravenous or intra-arterial abuse of these capsules,[3-5] and there are reports of ischaemia, in some cases necessitating amputation.[6-8] The *tablets* may also be liable to abuse; there has been a report of death after intravenous injection of a solution containing crushed temazepam tablets.[9] The manufacturers of a temazepam *elixir* considered that, because of its viscosity and its low strength relative to the liquid in the capsules, it had a low potential for intravenous abuse.[10] Nonetheless, there have been reports[3] of some drug abusers injecting large quantities of diluted elixir.

For mention of rhabdomyolysis associated with abuse of temazepam, see Effects on Skeletal Muscle, under Diazepam, p. 1066.2.

1. Farrell M, Strang J. Misuse of temazepam. *BMJ* 1988; 297: 1402.
2. Launchbury AP. Temazepam abuse. *Pharm J* 1990; 244: 749.
3. Ruben SM, Morrison CL. Temazepam misuse in a group of injecting drug users. *Br J Addict* 1992; 87: 1387–92.
4. Scott RN, *et al.* Intra-arterial temazepam. *BMJ* 1992; 304: 1630.
5. Adiseshiah M, *et al.* Intra-arterial temazepam. *BMJ* 1992; 304: 1630.
6. Blair SD, *et al.* Leg ischaemia secondary to non-medical injection of temazepam. *Lancet* 1991; 338: 1393–4.
7. Fox R, *et al.* Misuse of temazepam. *BMJ* 1992; 305: 253.
8. Feeney GFX, Gibbs HH. Digit loss following misuse of temazepam. *Med J Aust* 2002; 176: 380.
9. Vella EJ, Edwards CW. Death from pulmonary microembolization after intravenous injection of temazepam. *BMJ* 1993; 307: 26.
10. Drake J, Ballard R. Misuse of temazepam. *BMJ* 1988; 297: 1402.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that, although the effect of temazepam on breast-fed infants was unknown, its use by mothers during breast feeding might be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Temazepam was detected in breast milk in only one of 10 mothers given temazepam as a bedtime sedative;[2] temazepam was given in a dose of 10 to 20 mg and milk concentrations were measured about 15 hours after a dose. The authors considered that breast-fed neonates would ingest negligible amounts of temazepam.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Lebedevs TH, *et al.* Excretion of temazepam in breast milk. *Br J Clin Pharmacol* 1992; 33: 204–6.

Effects on the skin. Generalised lichenoid drug eruption that had persisted for 5 months in an elderly patient receiving therapy including temazepam resolved within 10 days of stopping the benzodiazepine.[1] Bullous eruptions associated with temazepam overdose have also been reported.[2]

1. Norris P, Sounex TS. Generalised lichenoid drug eruption associated with temazepam. *BMJ* 1986; 293: 510.
2. Verghese J, Merino J. Temazepam overdose associated with bullous eruptions. *Acad Emerg Med* 1999; 6: 1071.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, and UK licensed product information advises that temazepam should be avoided in severe cases. However, short-acting benzodiazepines such as temazepam may pose less risk in patients with hepatic impairment; in a study of 15 patients with cirrhosis and 16 healthy subjects, liver disease had no significant effect on the pharmacokinetic parameters or pattern of elimination of temazepam.[1]

1. Ghabril H, *et al.* The effects of age and chronic liver disease on the elimination of temazepam. *Eur J Clin Pharmacol* 1986; 30: 93–7.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Temazepam is fairly readily absorbed from the gastrointestinal tract, although the exact rate of absorption depends on the formulation. It is about 96% bound to plasma proteins. Temazepam is metabolised mainly in the liver; mean elimination half-lives of about 8 to 15 hours or longer have been reported. It is excreted mainly in the urine in the form of its inactive glucuronide conjugate together with small amounts of the demethylated derivative, oxazepam, also in conjugated form. Temazepam is distributed into breast milk.

Absorption and plasma concentration. Various oral temazepam formulations have been available worldwide. These included powder-filled hard gelatin capsules, liquid-filled soft gelatin capsules, semi-solid gel-filled soft gelatin capsules, and an elixir. There has been considerable debate over the comparative absorption profiles of temazepam from these formulations which have, in some cases, been modified over the years. It should be noted that pharmacokinetic studies of temazepam do not always clearly state the formulation used.

Temazepam 30 mg was given as a premedicant to 80 patients undergoing surgery in the form of capsules [type not stated] or elixir.[1] Mean peak plasma concentrations of about 800 nanograms/mL occurred 30 minutes after a dose of either formulation although there was wide interindividual variation in plasma concentrations. The evidence corresponded with previous suggestions that a plasma concentration of about 250 nanograms/mL or more was required to ensure sedation. The presence or absence of anxiety did not influence the absorption of the preparations.

1. Hosie HE, Nimmo WS. Temazepam absorption in patients before surgery. *Br J Anaesth* 1991; 66: 20–4.

Distribution into CSF. A study in 13 male patients showed a correlation between the unbound concentration of temazepam in plasma and the amount of temazepam detected in CSF.[1] The mean CSF to total plasma temazepam concentration ratio was 5.2.

1. Badcock NR. Plasma and cerebrospinal fluid concentrations of temazepam following oral drug administration. *Eur J Clin Pharmacol* 1990; 38: 153–5.

Metabolism. References.

1. Lockiskar A, Greenblatt DJ. Oxidative versus conjugative biotransformation of temazepam. *Biopharm Drug Dispos* 1990; 11: 499–506.

Sex differences. The elimination half-life was significantly longer at 16.8 hours among 17 women given temazepam 30 mg compared with 12.3 hours among 15 men.[1] The total clearance was also lower among women. After correction for differences in protein binding, unbound clearance was still lower in women than men but there was no significant effect of age on this parameter. Time to peak

plasma concentration and volume of distribution were not affected by the age or sex of the subjects.

1. Divoll M, *et al.* Effect of age and gender on disposition of temazepam. *J Pharm Sci* 1981; 70: 1104–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Normison; Temaze; Temtabs; ***Canad.***: Restoril; ***Fin.***: Tenox; ***Fr.***: Normison; ***Ger.***: Planum; Pronervon T†; Remestan; Temazep†; ***Gr.***: Euhypnos; Normison; Reposium; Tonirem; ***Hung.***: Signopam; ***Irl.***: Insomniger; Nortem; Tenox; ***Ital.***: Euipnos†; Normison; ***Neth.***: Normison; ***NZ***: Euhypnos; Normison; ***Pol.***: Signopam; ***Port.***: Normison; ***Rus.***: Signopam (Сигнопам); ***S.Afr.***: Normison; ***Switz.***: Normison; ***Thai.***: Euhypnos; ***USA***: Restoril.

Pharmacopoeial Preparations
BP 2014: Temazepam Oral Solution; Temazepam Tablets;
USP 36: Temazepam Capsules.

Tetrazepam *(BAN, pINN)*

CB-4261; Tetratsepaami; Tetrazepám; Tétrazépam; Tetrazepamas; Tetrazepamum; Тетразепам.
7-Chloro-5-(cyclohex-1-enyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.
$C_{16}H_{17}ClN_2O$=288.8
CAS — 10379-14-3.
ATC — M03BX07.
ATC Vet — QM03BX07.
UNII — FO92091VP8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tetrazepam). A light yellow or yellow crystalline powder. Practically insoluble in water; soluble in acetonitrile; freely soluble in dichloromethane. Protect from light.

Profile

Tetrazepam is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It has been used for its muscle relaxant properties in the treatment of muscle spasm; however, serious cutaneous reactions have been reported and this has led to the suspension of tetrazepam in the EU (see below for further details).

Effects on the skin. There have been case reports of cutaneous reactions to tetrazepam, including contact dermatitis,[1-4] erythema multiforme,[5] acute generalised exanthematous pustulosis,[6] and toxic epidermal necrolysis.[7] Of 9 patients who had had cutaneous reactions to tetrazepam none had reactions to diazepam, bromazepam, or lorazepam and in 5 cases where oral provocation tests were performed there were also no reactions.[8]

In April 2013, the European Pharmacovigilance Risk Assessment Committee (PRAC) reviewed[9] all available data on the risk of cutaneous reactions with tetrazepam, and its efficacy in licensed indications. It was found that half of all reported reactions were cutaneous; some of which were serious, life-threatening, or fatal, and included Stevens-Johnson syndrome and DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. These reactions were unpredictable and occurred at any stage during treatment, including after short-term therapy and at recommended doses. Moreover, the risk of cutaneous reactions was found to be higher with tetrazepam than with other benzodiazepines and the data on its efficacy were not sufficiently robust to support its use. Consequently, the European Medicines Agency suspended the marketing authorisation of tetrazepam in the EU.

1. Lepp U, *et al.* Occupational airborne contact allergy to tetrazepam. *Contact Dermatitis* 2003; 49: 260–1.
2. Perran M, *et al.* Occupational airborne contact dermatitis from sporadic exposure to tetrazepam during machine maintenance. *Contact Dermatitis* 2005; 52: 173–4.
3. Breuer K, *et al.* Occupational airborne contact allergy to tetrazepam in a geriatric nurse. *J Dtsch Dermatol Ges* 2009; 7: 896–8.
4. Vander Hulst K, *et al.* Occupational allergic contact dermatitis from tetrazepam in nurses. *Contact Dermatitis* 2010; 62: 303–8.
5. Cabrerizo Ballesteros S, *et al.* Erythema multiforme to tetrazepam. *J Investig Allergol Clin Immunol* 2007; 17: 205–6.
6. Thomas E, *et al.* Acute generalized exanthematous pustulosis due to tetrazepam. *J Investig Allergol Clin Immunol* 2008; 18: 119–22.
7. Delesalle F, *et al.* Toxic epidermal necrolysis caused by tetrazepam. *Int J Dermatol* 2006; 45: 480.
8. Barbaud A, *et al.* No cross-reactions between tetrazepam and other benzodiazepines: a possible chemical explanation. *Contact Dermatitis* 2009; 61: 53–6.
9. EMEA. Tetrazepam-containing medicines (issued 24th April, 2013). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Tetrazepam_containing_medicinal_products/human_referral_prac_000015.jsp&mid=WC0b01ac05805c516f (accessed 04/12/13)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Myolastan†; ***Belg.***: Epsipam†; Myolastan†; ***Cz.***: Myolastan†; ***Fr.***: Myolastan†; Panos†; ***Ger.***: Musapam†; Musaril†; Myospasmal†; Rilex†; Tetra-saar†; Tetrazep†; ***Mex.***: Miolastan; ***Pol.***: Miozepam†; Myolastan†; Myopam†; Tetraratio†; ***Spain***: Myolastan†.

Thioproperazine Mesilate *(BANM, rINNM)*

Mesilato de tioproperazina; RP-7843; SKF-5883; Thioproperazine Dimethanesulphonate; Thiopropérazine, Méslate de; Thioproperazine Mesylate; Thioproperazine Methanesulphonate; Thioproperazini Mesilas; Tioproperazina, mesilato de; Тиопропиразина Мезилат.
NN-Dimethyl-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine-2-sulphonamide dimethanesulphonate.
$C_{22}H_{30}N_4O_2S_2.2CH_4O_3S$=638.8
CAS — 316-81-4 (thioproperazine); 2347-80-0 (thioproperazine mesilate).
ATC — N05AB08.
ATC Vet — QN05AB08.
UNII — 71P630M192.

Pharmacopoeias. In *Fr.*

Profile

Thioproperazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has a piperazine side-chain. It is used in the treatment of schizophrenia (p. 1031.3), mania (see Bipolar Disorder, p. 397.2), and other psychoses. Thioproperazine is given as the mesilate although doses are expressed in terms of the base; thioproperazine mesilate 7.2 mg is equivalent to about 5 mg of thioproperazine. Initial daily doses of 5 mg are given orally, increased as necessary; the usual effective dosage is 30 to 40 mg daily. In severe or resistant cases daily doses of 90 mg or more have been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Majeptil; ***Gr.***: Majeptil; ***Rus.***: Majeptil (Мажептил).

Thioridazine *(BAN, USAN, rINN)*

Thioridazin; Thioridazinum; Tioridatsiini; Tioridazin; Tioridazina; Tioridazinas; TP-21; Тиоридазин.
10-[2-(1-Methyl-2-piperidyl)ethyl]-2-methylthiophenothiazine.
$C_{21}H_{26}N_2S_2$=370.6
CAS — 50-52-2.
ATC — N05AC02.
ATC Vet — QN05AC02.
UNII — N3D6TG58NI.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Thioridazine). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Thioridazine). A white to slightly yellow crystalline or micronised powder; odourless or having a faint odour. Practically insoluble in water; freely soluble in dehydrated alcohol and in ether; very soluble in chloroform. Protect from light.

Thioridazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tioridazina; Thioridazin hydrochlorid; Thioridazine, chlorhydrate de; Thioridazinhydrochlorid; Thioridazini Hydrochloridum; Tioridatsiinihydrokloridi; Tioridazina, hidrocloruro de; Tioridazinhidroklorid; Tioridazinhydroklorid; Tioridazino hidrochloridas; Tiorydazny chlorowodorek; Tiorydazyny chlorowodorek; Тиоридазина Гидрохлорид.
$C_{21}H_{26}N_2S_2.HCl$=407.0
CAS — 130-61-0.
ATC — N05AC02.
ATC Vet — QN05AC02.
UNII — 4WCI67NK8M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Thioridazine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Thioridazine Hydrochloride). A white to slightly yellow granular powder having a slight odour. Freely soluble in water, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. For a warning about incompatibility between thioridazine hydrochloride solution (*Mellaril; Novartis, USA*) and carbamazepine suspension (*Tegretol; Novartis, USA*), see p. 512.2.

Uses and Administration

Thioridazine is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperidine side-chain and, unlike chlorpromazine, has little antiemetic activity.

The use of thioridazine has been restricted to the treatment of schizophrenia (p. 1031.3) in patients who fail to show an adequate response to treatment with other antipsychotics. Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential; it has been withdrawn in some countries, including the UK.

For all patients starting thioridazine it is recommended that ECG and electrolyte screening are performed periodically (see Precautions, p. 1111.1 for details).

Thioridazine is given orally as the hydrochloride or the base, and doses may be expressed in terms of either. In some countries, doses of oral liquid preparations have been given in terms of the base, whereas those of the tablets have been given as the hydrochloride. In the USA, all doses are given in terms of the hydrochloride. Thioridazine 22.8 mg is equivalent to about 25 mg of thioridazine hydrochloride.

In the treatment of schizophrenia thioridazine hydrochloride should be started at the usual dose of 50 to 100 mg three times daily and slowly titrated upwards to a maximum of 800 mg daily if necessary; doses should be reduced once effective control is achieved. The daily dosage range is 200 to 800 mg, which may be given in 2 to 4 divided doses. It has been recommended that increases in doses should be no more than 100 mg weekly.

Thioridazine should be given in lower initial doses to patients with a low body-mass or those with hepatic or renal impairment; dosage increases should also be more gradual.

In those patients who require withdrawal of thioridazine, the dose should be gradually reduced over 1 to 2 weeks to avoid symptoms such as gastrointestinal disorders, dizziness, anxiety, and insomnia that are sometimes seen after abruptly stopping high-dose or long-term treatment.

References.

1. Fenton M, *et al.* Thioridazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/03/08).

Adverse Effects and Treatment

As for Chlorpromazine, p. 1047.2.

Thioridazine has been associated with a higher incidence of antimuscarinic effects, but lower incidence of extrapyramidal effects than chlorpromazine. It may also be less sedating. However, it is more likely to induce hypotension and there is an increased risk of cardiotoxicity and dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use has been restricted (see Precautions, and Uses and Administration, p. 1111.1 and above, respectively). Sexual dysfunction also appears to be more frequent with thioridazine.

Pigmentary retinopathy characterised by reduced visual acuity, brownish colouring of vision, and impairment of night vision has been seen particularly in patients taking large doses.

Effects on the cardiovascular system. Between 1964 and 2001, the UK CSM received 42 reports of suspected heart rate and rhythm disorders associated with thioridazine.[1] There were 21 fatalities reported out of 39 cases where the outcome was known.

See also under Chlorpromazine, p. 1047.3.

1. CSM/MCA. QT interval prolongation with antipsychotics. *Current Problems* 2001; 27: 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 12/05/06)

Hypersensitivity. Pruritus and erythematous rash on the genitals of a woman after sexual intercourse were found to be due to thioridazine present in the seminal fluid of her husband, who was taking 100 mg daily at night.[1]

1. Sell MB. Sensitization to thioridazine through sexual intercourse. *Am J Psychiatry* 1985; 142: 271–2.

Overdosage. Rhabdomyolysis has been reported in a patient after overdosage with thioridazine.[1] Twenty-four hours after taking 9.4 g of thioridazine the patient presented with difficulty in moving and speaking. On examination he had swelling and tenderness over his upper arms, thighs, and calves. Ataxia and transient dysarthria were attributed to generalised muscle weakness. Other

effects were consistent with antimuscarinic effects of thioridazine. He had no signs of neuroleptic malignant syndrome but his urine contained myoglobin. The patient was treated with gastric lavage, activated charcoal, and rehydration. Serum biochemistry returned to normal over 1 week and the muscle tenderness and weakness disappeared.

1. Nankivell BJ, *et al.* Rhabdomyolysis induced by thioridazine. *BMJ* 1994; 309: 378.

Precautions

As for Chlorpromazine, p. 1050.3. Thioridazine should not be used in patients with clinically significant cardiac disorders, uncorrected hypokalaemia or other electrolyte imbalance, with known or suspected QT prolongation or a family history of QT prolongation, or with a history of ventricular arrhythmias including torsade de pointes. Use is also contra-indicated in patients known to have reduced activity of the cytochrome P450 isoenzyme CYP2D6, which is responsible for thioridazine metabolism. Use with drugs liable to interfere with the metabolism of thioridazine, with other drugs known to prolong the QT interval, and with drugs likely to cause electrolyte imbalance should also be avoided (see under Interactions, below).

For all patients starting thioridazine it is recommended that a baseline ECG and electrolyte screening are performed. An ECG should also be repeated before each dose increase, 1 week after the maximum therapeutic dose has been reached, and at 6-monthly intervals in those who continue treatment. Serum electrolyte concentrations should also be monitored periodically during treatment and any imbalance corrected.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thioridazine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3. The metabolism of thioridazine is mediated by the cytochrome P450 isoenzyme CYP2D6; thioridazine itself is also an inhibitor of CYP2D6. Therefore, there is the potential for interactions between thioridazine and other drugs that inhibit or act as a substrate for this enzyme; such drugs should not be given with thioridazine. Some examples include antiarrhythmics, certain antidepressants including the SSRIs and tricyclics, certain antipsychotics, beta blockers, HIV-protease inhibitors, and opioids.

Use with other drugs known to prolong the QT interval such as class IA and class III antiarrhythmics, tricyclic antidepressants, and some other antipsychotics should also be avoided, as should use with those drugs known to cause electrolyte imbalance.

Pharmacokinetics

The pharmacokinetics of thioridazine appear to be generally similar to those of chlorpromazine (p. 1053.3). Thioridazine is metabolised by the cytochrome P450 isoenzyme CYP2D6. Its main active metabolite is mesoridazine (p. 1084.2); another metabolite, sulforidazine, also has some activity. Thioridazine and its active metabolites are reported to be highly bound to plasma proteins (more than 95%). The plasma half-life of thioridazine has been estimated to be about 4 to 10 hours. It also crosses the placenta and is distributed into breast milk.

References.

1. Mårtensson E, Roos B-E. Serum levels of thioridazine in psychiatric patients and healthy volunteers. *Eur J Clin Pharmacol* 1973; 6: 181–6.
2. Axelsson R, Mårtensson E. Serum concentration and elimination from serum of thioridazine in psychiatric patients. *Curr Ther Res* 1976; 19: 242–65.

Metabolism. In 10 psychiatric patients stabilised on thioridazine, therapy was replaced by equipotent doses of the side-chain sulfoxide (mesoridazine) and side-chain sulfone (sulforidazine) metabolites of thioridazine.[1] Both metabolites were shown to have an antipsychotic effect, the dose of each required being about two-thirds that of thioridazine. The serum half-lives were thioridazine 21 hours, mesoridazine 16 hours, and sulforidazine 13 hours. Apathy, depression, and restlessness gradually developed during treatment with the 2 metabolites and they could not be used for any length of time. Extrapyramidal symptoms, hypersalivation, and drowsiness were more common with the metabolites; 2 patients had epileptic seizures, and 1 receiving sulforidazine developed probable cholestatic jaundice.

There is some evidence that the metabolism of thioridazine is influenced by debrisoquine hydroxylation phenotype.[2] A single-dose study in 19 healthy male subjects found slower formation of mesoridazine, and hence higher serum-thioridazine concentrations in poor debrisoquine hydroxylators compared with extensive hydroxylators. Formation of thioridazine ring-sulfoxide appeared to be compensatorily increased in slow hydroxylators.

1. Axelsson R. On the serum concentrations and antipsychotic effects of thioridazine, thioridazine side-chain sulfoxide and thioridazine side-chain sulfone, in chronic psychotic patients. *Curr Ther Res* 1977; 21: 587–605.
2. von Bahr C, *et al.* Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. *Clin Pharmacol Ther* 1991; 49: 234–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Melleril; *Austral.*: Aldazine†; *Braz.*: Melleril; Unitidazin; *Chile*: Simultan; *China*: Ridazine (利达新); *Ger.*: Melleril; *Gr.*: Detril; Elperil; Melleril; *India*: Melleril; Melozine; Thioril; *Indon.*: Melleril†; *Israel*: Ridazin; *Mex.*: Dazithin; Melleril; *NZ*: Aldazine†; *Philipp.*: Thiozine; *Rus.*: Sonapax (Сонапакс); Thiodazine (Тиодазин); Thioril (Тиорил); Tison (Тисон); *Thai.*: Dazine-P; Ridazine; Thiomed; Thiosia; *Turk.*: Mellerettes; Melleril; *Ukr.*: Ridazine (Ридазин)†; Sonapax (Сонапакс).

Pharmacopoeial Preparations
USP 36: Thioridazine Hydrochloride Oral Solution; Thioridazine Hydrochloride Tablets; Thioridazine Oral Suspension.

Tiapride Hydrochloride *(BANM, rINNM)*

FLO-1347; Hidrocloruro de tiaprida; Tiaprida, hidrocloruro de; Tiapride, Chlorhydrate de; Tiaprid-hidroklorid; Tiapridhydrochlorid; Tiaprid-hydrochlorid; Tiapridhydroklorid; Tiapridi hydrochloridum; Tiapridihydrokloridi; Tiaprido hidrochloridas; Тиаприда Гидрохлорид.

N-(2-Diethylaminoethyl)-2-methoxy-5-methylsulphonylbenzamide hydrochloride.

$C_{15}H_{24}N_2O_4S,HCl$=364.9

CAS — 51012-32-9 (tiapride); 51012-33-0 (tiapride hydrochloride).

ATC — N05AL03.

ATC Vet — QN05AL03.

UNII — 25N106WEDO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tiapride Hydrochloride). A white or almost white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. A 5% solution in water has a pH of 4.0 to 6.0.

Uses and Administration

Tiapride is a substituted benzamide with general properties similar to those of sulpiride (p. 1107.3).

It is usually given as the hydrochloride in the management of behavioural disorders (below), to treat dyskinesias (see Extrapyramidal Disorders, below), and as an analgesic. Doses are expressed in terms of the equivalent amount of base; tiapride hydrochloride 222.2 mg is equivalent to about 200 mg of tiapride. Oral doses of 100 to 300 mg daily are usually given for behavioural disorders; higher daily doses have been used in the management of dyskinesias. Oral doses of 200 to 400 mg daily may be given for severe intractable pain. Tiapride hydrochloride has also been given by intramuscular or intravenous injection.

Disturbed behaviour. For a discussion of the management of disturbed behaviour including limitations on the use of antipsychotics, see p. 1030.2.

References.

1. Gutzmann H, *et al.* Measuring the efficacy of psychopharmacological treatment of psychomotoric restlessness in dementia: clinical evaluation of tiapride. *Pharmacopsychiatry* 1997; 30: 6–11.
2. Allain H, *et al.* Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. *Psychopharmacology (Berl)* 2000; 148: 361–6.

Extrapyramidal disorders. Tiapride has been tried in the treatment of antipsychotic-induced tardive dyskinesia (p. 1049.3), but, as with all antipsychotics, improvement may only be short-term.

Tiapride has also been tried in the treatment of Tourette's syndrome (see Tics, p. 1030.1).

For reference to the use of tiapride in suppressing the adverse effects of levodopa on respiration, see p. 905.3.

CHOREA. Antipsychotics have some action against choreiform movements as well as being of use to control the behavioural disturbances of Huntington's chorea, and tiapride has been quite widely used for this purpose. For a discussion of the management of various choreas, see p. 1029.3.

References.

1. Roos RAC, *et al.* Tiapride in the treatment of Huntington's chorea. *Acta Neurol Scand* 1982; 65: 45–50.
2. Deroover J, *et al.* Tiapride versus placebo: a double-blind comparative study in the management of Huntington's chorea. *Curr Med Res Opin* 1984; 9: 329–38.

Substance dependence. An early review[1] concluded that the role of tiapride in acute *alcohol* withdrawal (p. 1735.1) was likely to be limited as patients at risk of severe reactions would still require adjunctive therapy for the control of hallucinations and seizures. In one study,[2] following detoxification, tiapride appeared to help, to some degree, to alleviate distress, improve abstinence and drinking behaviour, and facilitate reintegration within society but a subsequent study[3] failed to find any advantage over placebo. Interest in its use with carbamazepine continues.[4-6]

1. Peters DH, Faulds D. Tiapride: a review of its pharmacology and therapeutic potential in the management of alcohol dependence syndrome. *Drugs* 1994; 47: 1010–32.
2. Shaw GK, *et al.* Tiapride in the prevention of relapse in recently detoxified alcoholics. *Br J Psychiatry* 1994; 165: 515–23.
3. Bender S, *et al.* The efficacy of the dopamine D_2/D_3 antagonist tiapride in maintaining abstinence: a randomized, double-blind, placebo-controlled trial in 299 alcohol-dependent patients. *Int J Neuropsychopharmacol* 2007; 10: 653–60.
4. Franz M, *et al.* Treatment of alcohol withdrawal: tiapride and carbamazepine versus clomethiazole: a pilot study. *Eur Arch Psychiatry Clin Neurosci* 2001; 251: 185–92.
5. Lucht M, *et al.* Alcohol withdrawal treatment in intoxicated vs non-intoxicated patients: a controlled open-label study with tiapride/carbamazepine, clomethiazole and diazepam. *Alcohol Alcohol* 2003; 38: 168–75.
6. Soyka M, *et al.* Efficacy and safety of outpatient alcohol detoxification with a combination of tiapride/carbamazepine: additional evidence. *Pharmacopsychiatry* 2006; 39: 30–4.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2.

Effects on the cardiovascular system. Torsade de pointes developed after a single dose of tiapride in an elderly patient with cardiac disease, a known risk factor for such arrhythmias.[1]

1. Iglesias E, *et al.* Tiapride-induced torsade de pointes. *Am J Med* 2000; 109: 509.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Tiapride is rapidly absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is excreted largely unchanged in the urine. The plasma half-life is reported to range from 3 to 4 hours. It is thought to be distributed into breast milk on the basis of *animal* studies.

The steady-state pharmacokinetics of tiapride have been studied in 5 elderly patients with tardive dyskinesia, and in 2 patients with Huntington's chorea.[1] All patients received oral tiapride 100 mg three times daily for 7 days. The mean peak plasma concentration of tiapride was 1.47 micrograms/mL, achieved a mean of 1.4 hours after dosing, and the mean elimination half-life was 3.8 hours. These values did not differ significantly from those previously reported in younger healthy subjects, although renal clearance was slightly lower in these patients. About half of the dose of tiapride was excreted unchanged by the kidneys; a metabolite, probably *N*-monodesethyltiapride was detected in the urine but its identity was not confirmed.

1. Roos RAC, *et al.* Pharmacokinetics of tiapride in patients with tardive dyskinesia and Huntington's disease. *Eur J Clin Pharmacol* 1986; 31: 191–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Delpral; *Belg.*: Tiapridal; *Braz.*: Tiapridal; *Chile*: Sereprid; *China*: Luo Yi (罗逸); Shang Yan (尚岩); Wei Qi (维奇); *Cz.*: Tiapra; Tiapralan; Tiapridal; *Fr.*: Tiapridal; *Ger.*: Tiapridex†; *Gr.*: Tiapridal; *Hung.*: Tiager; Tiapridal; *Ital.*: Italprid; Sereprile; *Jpn*: Gramalil; *Neth.*: Elbaprid†; Tiacob†; Tiapridal; Tiazet; *Pol.*: Tiapridal; *Port.*: Tiapridal; *Rus.*: Tiapridal (Тиапридал); *Singapore*: Tiapridal; *Spain*: Tiaprizal; *Switz.*: Tiapridal.

Timiperone *(rINN)*

DD-3480; Timiperona; Timipérone; Timiperonum; Тимиперон.

4'-Fluoro-4-[4-(2-thioxo-1-benzimidazolinyl)piperidino]butyrophenone.

$C_{22}H_{24}FN_3OS$=397.5

CAS — 57648-21-2

UNII — 626DQ7N19L

Profile

Timiperone is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1). It is given orally or by intravenous or intramuscular injection in the treatment of schizophrenia. Timiperone has also been given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Celmanil; Tolopelon.

Tiotixene *(BAN, rINN)*

NSC-108165; P-4657B; Thiothixene (USAN); Thiothixene; Tiotikseeni; Tiotixen; Tiotixène; Tiotixeno; Tiotixenum; Тиотиксен.

(*Z*)-*NN*-Dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulphonamide.

$C_{23}H_{29}N_3O_2S_2$=443.6

CAS — 5591-45-7; 3313-26-6 (tiotixene Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

UNII — 7318FJ13YJ.

Pharmacopoeias. In *US*.

USP 36: (Thiothixene). White to tan, practically odourless, crystals. Practically insoluble in water; soluble 1 in 110 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 120 of ether; slightly soluble in acetone and in methyl alcohol. Store in airtight containers. Protect from light.

Tiotixene Hydrochloride *(BANM, rINNM)*

CP-12252-1; Hidrocloruro de tiotixeno; Thiothixene Hydrochloride (USAN); Tiotixène, Chlorhydrate de; Tiotixeni Hydrochloridum; Tiotixeno, hidrocloruro de; Тиотиксена гидрохлорид.

$C_{23}H_{29}N_3O_2S_2.2HCl.2H_2O$=552.6

CAS — 58513-59-0 (anhydrous tiotixene hydrochloride); 49746-04-5 (anhydrous tiotixene hydrochloride, Z-isomer); 22189-31-7 (tiotixene hydrochloride dihydrate); 49746-09-0 (tiotixene hydrochloride dihydrate, Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

UNII — B3CRJ1EWJU.

Pharmacopoeias. In *US*, which permits both the dihydrate and the anhydrous form.

USP 36: (Thiothixene Hydrochloride). It is anhydrous ($C_{23}H_{29}N_3O_2S_2.2HCl$ = 516.5) or contains two molecules of water of hydration. A white or practically white crystalline powder having a slight odour. Soluble 1 in 8 of water, 1 in 270 of dehydrated alcohol, and 1 in 280 of chloroform; practically insoluble in acetone, in ether, and in benzene. Store in airtight containers. Protect from light.

Stability. A combination of the stabilisers hydroxyquinoline sulfate and vanillin could protect tiotixene from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; 67: 169–75.

Uses and Administration

Tiotixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain. It is used in the treatment of psychoses including schizophrenia (p. 1031.3). Tiotixene is given orally as the base or hydrochloride; it has also been given by intramuscular injection as the hydrochloride. Doses are expressed in terms of the base. Tiotixene 1 mg is equivalent to about 1.2 mg of tiotixene hydrochloride.

The usual initial oral dose is 2 mg three times daily (or 5 mg twice daily in more severe conditions) gradually increasing to 20 to 30 mg daily if necessary; once-daily dosage may be adequate. In severe or resistant psychoses doses of up to 60 mg daily may be given. A dose of 4 mg two to four times daily increased if necessary to a maximum of 30 mg daily has been given intramuscularly.

Tiotixene should be given in reduced dosage to elderly or debilitated patients.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Tiotixene is less likely to cause sedation but extrapyramidal effects are more frequent.

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

In 15 adequately controlled schizophrenic patients receiving oral tiotixene 15 to 60 mg daily in 2, 3, or 4 divided doses, plasma concentrations were found to be in the relatively narrow range of 10 to 22.5 nanograms/mL 126 to 150 minutes after the last daily dose despite the fourfold difference in dosage.[1] Investigations in a further 5 patients indicated that peak plasma concentrations were obtained about 1 to 3 hours after a dose, indicating rapid absorption with an absorption half-time of about 30 minutes. There was an early plasma half-life of about 210 minutes and a late half-life of about 34 hours; resurgence of drug concentrations in some subjects might have been due to enterohepatic recycling.

1. Hobbs DC, *et al.* Pharmacokinetics of thiothixene in man. *Clin Pharmacol Ther* 1974; 16: 473–8

Metabolism. There has been a study[1] indicating that tiotixene may induce its own metabolism.

1. Bergling R, *et al.* Plasma levels and clinical effects of thioridazine and thiothixene. *J Clin Pharmacol* 1975; 15: 178–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Navane†; *Canad.*: Navane; *Hong Kong*: Navane†; *NZ*: Thixit†; *USA*: Navane.

Pharmacopoeial Preparations

USP 36: Thiothixene Capsules; Thiothixene Hydrochloride for Injection; Thiothixene Hydrochloride Injection; Thiothixene Hydrochloride Oral Solution.

Tofisopam *(rINN)*

EGYT-341; Tofisopaami; Tofisopamum; Tofizopam; Тофизопам.

1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine.

$C_{22}H_{26}N_2O_4$=382.5

CAS — 22345-47-7.

ATC — N05BA23.

ATC Vet — QN05BA23.

UNII — UZC80HAU42.

Pharmacopoeias. In *Jpn*.

Profile

Tofisopam is a short-acting 2,3-benzodiazepine related structurally to the 1,4-benzodiazepines such as diazepam (p. 1063.2) and sharing some of the same actions. It is reported, however, to be largely lacking in the sedative, anticonvulsant, and muscle relaxant properties of the conventional benzodiazepines. Tofisopam has been given orally in the short-term treatment of anxiety disorders. The *R*-(+)-isomer, dextofisopam, is under investigation in the treatment of irritable bowel syndrome.

References.

1. Leventer SM, *et al.* Clinical trial: dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. *Aliment Pharmacol Ther* 2008; 27: 197–206.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Grandaxin; *Hung.*: Grandaxin; *Jpn*: Bydaxin; Clasopan†; Cobandaxin; Emandaxin†; Grandaxin; Granpam; Hymidin; Myronin; Tofiel; Tofilsin; Tofis; Tolbanasin; Tronheim; Tsurubel; *Rus.*: Grandaxin (Грандаксин); *Thai.*: Grandaxin.

Triacetonamine Tosilate

Tempidon; Триацетонамина Тозилат.

2,2,6,6-Tetramethyl-4-piperidone toluene-4-sulfonate.

$C_{16}H_{25}NO_4S$=327.4

CAS — 826-36-8 (triacetonamine); 29334-13-2 (triacetonamine tosilate).

Profile

Triacetonamine tosilate has anxiolytic actions and is used in combination preparations with analgesics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Tempalgin (Темпалгин); Tempanginol (Темпангинол); *Ukr.*: Tempalgin (Темпалгин); Tempanal (Темпанал).

Triazolam *(BAN, USAN, rINN)*

Clorazolam; Triatsolaami; Triazolamum; U-33030; Триазолам.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine.

$C_{17}H_{12}Cl_2N_4$=343.2

CAS — 28911-01-5.

ATC — N05CD05.

ATC Vet — QN05CD05.

UNII — 1HM943223R.

Pharmacopoeias. In *Chin.* and *US*.

USP 36: (Triazolam). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 1000 of alcohol, 1 in 25 of chloroform, and 1 in 600 of 0.1*N* hydrochloric acid.

Uses and Administration

Triazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p. 1063.3). It is used as a hypnotic in the short-term (up to 2 weeks) management of insomnia (p. 1033.2) in oral doses of 125 to 250 micrograms at night; doses of up to 500 micrograms at night have been used for resistant cases but these may be associated with an increased risk of severe adverse effects (see Effects on Mental Function, below). Initial doses of 125 micrograms at night have been suggested for elderly or debilitated patients, increased up to a maximum of 250 micrograms only if necessary.

Administration in hepatic or renal impairment. See under Precautions, p. 1113.1.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects and Treatment

As for Diazepam, p. 1065.3.

Effects on the liver. A 44-year-old man developed severe pruritus with jaundice which subsequently proved fatal. Liver histology showed intense cholestasis. Triazolam was considered to be the most likely cause.[1]

1. Cobden I, *et al.* Fatal intrahepatic cholestasis associated with triazolam. *Postgrad Med J* 1981; 57: 730–1.

Effects on mental function. The effects of triazolam on mental function have been controversial since van der Kroef first described in 1979 a range of symptoms including anxiety, amnesia, depersonalisation and derealisation, depression, paranoia, and severe suicidal tendencies that he had seen in 25 patients and attributed to triazolam.[1] This led to suspension of triazolam in the Netherlands (re-approved in 1990) and removal of the 1-mg tablet from other markets. Continued reporting of similar symptoms of cognitive impairment with triazolam resulted in withdrawal of the 500-microgram dosage form in several countries in 1987 and 1988 and in a gradual reduction of recommended dosage from 1 mg at night down to 125 to 250 micrograms at night. Subsequently, all strengths of triazolam were withdrawn from the UK[2] and some other markets in 1991. Opinion remained divided over the adverse effects of triazolam, the main issues being its propensity to cause adverse effects relative to other benzodiazepines and whether its risk-benefit ratio is acceptable to justify its continued use.[3,4]

Others[5] have reviewed spontaneous adverse effects reported to the FDA for triazolam, temazepam, and flurazepam. Daytime sedation was noted with all three, but triazolam caused more agitation, confusion, hallucinations, and amnesia. Such effects occurred frequently with the 250-microgram dose as well as with the 500-microgram dose. Similar results were obtained after analysis of reports for triazolam and temazepam in the first 7 years of marketing, although the possibility that selection factors were producing higher reporting rates for triazolam could not be entirely excluded.[6] When triazolam 500 micrograms, lormetazepam 2 mg, or placebo, was given to groups of 40 patients for 25 nights the greatest frequency of daytime anxiety, panic, derealisation, and paranoia was noted with triazolam.[7] Another study[8] found a greater total number of reports of memory impairment or amnesia after nightly doses of triazolam 500 micrograms compared with temazepam 30 mg. Triazolam also impaired delayed, but not immediate, memory recall. Similar cases of memory impairment occurring with triazolam at doses of 125 and 250 micrograms have reportedly been submitted to the UK CSM.[2] The emergence of daytime symptoms after more than a few days' treatment with triazolam could be attributed to rebound or withdrawal phenomena occurring as a result of rapid elimination of the drug.

As regards the risk-benefit ratio of triazolam some have questioned the hypnotic efficacy of the drug at a dose of

250 micrograms and consider that reduction of the dose has decreased efficacy more than adverse effects.[3]

In defence of triazolam, the FDA and the manufacturers (*Upjohn*) have considered epidemiological studies which, unlike the FDA spontaneous reporting scheme, have been unable to find a substantial difference in its adverse effects compared with other benzodiazepines except, perhaps, in the incidence of amnesia.[9] Retrospective studies[10,11] claiming similar findings have been the subject of criticism.[12-14] Other workers have cited studies indicating benefit of triazolam 250 micrograms for the treatment of insomnia.[15] A review by the US Institute of Medicine found that triazolam was safe when given in a dose of 250 micrograms daily for 7 to 10 days but called for studies of lower doses and of long-term use.[16]

1. Van der Kroef C. Reactions to triazolam. *Lancet* 1979; ii: 526.
2. Anonymous. The sudden withdrawal of triazolam—reasons and consequences. *Drug Ther Bull* 1991; 29: 89–90.
3. O'Donovan MC, McGuffin P. Short acting benzodiazepines. *BMJ* 1993; 306: 945–6.
4. Ghaeli P, *et al.* Triazolam treatment controversy. *Ann Pharmacother* 1994; 28: 1038–40.
5. Bixler EO, *et al.* Adverse reactions to benzodiazepine hypnotics: spontaneous reporting system. *Pharmacology* 1987; 35: 286–300.
6. Wysowski DK, Barash D. Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's spontaneous reporting system. *Arch Intern Med* 1991; 151: 2003–8.
7. Adam K, Oswald I. Can a rapidly-eliminated hypnotic cause daytime anxiety? *Pharmacopsychiatry* 1989; 22: 115–19.
8. Bixler EO, *et al.* Next-day memory impairment with triazolam use. *Lancet* 1991; 337: 827–31.
9. Drucker RF, MacLeod N. Benzodiazepines. *Pharm J* 1989; 243: 508.
10. Hindmarch I, *et al.* Adverse events after triazolam substitution. *Lancet* 1993; 341: 55.
11. Rothschild AJ, *et al.* Triazolam and disinhibition. *Lancet* 1993; 341: 186.
12. Hawley CJ, *et al.* Adverse events after triazolam substitution. *Lancet* 1993; 341: 567.
13. Vela-Bueno A. Adverse events after triazolam substitution. *Lancet* 1993; 341: 567.
14. Kales A, *et al.* Adverse events after triazolam substitution. *Lancet* 1993; 341: 567–8.
15. Gillin JC, Byerley WF. Diagnosis and management of insomnia. *N Engl J Med* 1990; 323: 487.
16. Ault A. FDA advisers find no major Halcion dangers. *Lancet* 1997; 350: 1760.

Precautions

As for Diazepam, p. 1066.3.

Hepatic impairment. Cirrhosis decreased the apparent oral clearance of triazolam to an extent depending on the severity of the liver disease.[1] An initial dose of 125 micrograms was suggested for patients with severe liver dysfunction. It was suggested that the relative lack of effect that mild to moderate cirrhosis had on the metabolism of oral triazolam might be due to some first-pass metabolism occurring in the intestinal wall.[2]

1. Kroboth PD, *et al.* Nighttime dosing of triazolam in patients with liver disease and normal subjects: kinetics and daytime effects. *J Clin Pharmacol* 1987; 27: 555–60.
2. Robin DW, *et al.* Triazolam in cirrhosis: pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1993; 54: 630–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies triazolam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/03/11)

Renal impairment. Peak plasma-triazolam concentrations were lower in 11 dialysis patients compared with 11 controls.[1] It was postulated that a relatively high basal gastric acid secretion in dialysis patients could result in hydrolysis and opening of the ring structure of triazolam effectively reducing its systemic availability. Giving an antacid could reverse this effect. Renal failure had no other effect on the pharmacokinetics of triazolam which could probably be given in usual doses.

1. Kroboth PD, *et al.* Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics. *Br J Clin Pharmacol* 1985; 19: 839–42.

Interactions

As for Diazepam, p. 1068.1.

Pharmacokinetics

Triazolam is rapidly and nearly completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within 2 hours of an oral dose. Triazolam has a plasma elimination half-life ranging from 1.5 to 5.5 hours. It is reported to be about 89% bound to plasma proteins. Hydroxylation of triazolam in the liver is mediated by the cytochrome P450 isoenzyme CYP3A4. Triazolam is excreted in the urine mainly in the form of its conjugated metabolites with only small amounts appearing unchanged. Distribution of triazolam and its metabolites into milk has been found in studies in *rats*.

References.
1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; 16: 337–64.
2. Greenblatt DJ, *et al.* Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin Pharmacol Ther* 2004; 76: 467–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Halcion; ***Austria***: Halcion; ***Belg.***: Halcion; ***Canad.***: Apo-Triazo; ***Chile***: Balidon; Somese; ***China***: Hanlexin (酣乐欣); ***Denm.***: Halcion; ***Fin.***: Halcion; ***Gr.***: Halcion; ***Hong Kong***: Halcion; ***Irl.***: Halcion; Trilam†; ***Israel***: Halcion†; ***Ital.***: Halcion; Songar; Zotrilax†; ***Malaysia***: Inzolam; Somese; ***Mex.***: Halcion; ***NZ***: Halcion; Hypam; ***Port.***: Halcion; ***Rus.***: Halcion (Хальцион); ***S.Afr.***: Halcion; ***Spain***: Halcion; ***Swed.***: Halcion; ***Switz.***: Halcion; ***Thai.***: Halcion; Trialam; Trycam; ***USA***: Halcion; ***Venez.***: Somese.

Pharmacopoeial Preparations
USP 36: Triazolam Tablets.

Triclofos Sodium *(BANM, USAN, rINNM)*

Natrii Triclofosum; Sch-10159; Sodium Triclofos; Triclofós sódico; Triclofos Sodique; Натрий Триклофос.

Sodium 2,2,2-trichloroethyl hydrogen orthophosphate.

$C_2H_3Cl_3NaO_4P$=251.4

CAS — 306-52-5 (triclofos); 7246-20-0 (triclofos sodium).

ATC — N05CM07.

ATC Vet — QN05CM07.

UNII — 9F90KA5Q8U.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2014: (Triclofos Sodium). A white or almost white, odourless or almost odourless, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 3.0 to 4.5.

Profile

Triclofos sodium has hypnotic and sedative actions similar to those of cloral hydrate (p. 1055.2) but it causes less gastric irritation; also, it is not corrosive to skin and mucous membranes. It has been used similarly in the short-term management of insomnia and for sedation of children before painless procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Tricloryl; ***Israel***: Triclonam.

Pharmacopoeial Preparations
BP 2014: Triclofos Oral Solution.

Trifluoperazine Hydrochloride

(BANM, rINNM)

Hidrocloruro de trifluoperazina; Trifluoperazin Hidroklorür; Trifluoperazin hydrochlorid; Trifluoperazina, hidrocloruro de; Trifluoperazindihydrochlorid; Trifluopérazine, Chlorhydrate de; Trifluoperazinhidroklorid; Trifluoperazinhydroklorid; Trifluoperazini Hydrochloridum; Trifluoperazinio hidrochloridas; Trifluoperazyny chlorowodorek; Trifluoriperatsiinihydroklorid; Triphthazinum; Трифлуоперазина Гидрохлорид.

10-[3-(4-Methylpiperazin-1-yl)propyl]-2-trifluoromethylphenothiazine dihydrochloride.

$C_{21}H_{24}F_3N_3S,2HCl$=480.4

CAS — 117-89-5 (trifluoperazine); 440-17-5 (trifluoperazine hydrochloride).

ATC — N05AB06.

ATC Vet — QN05AB06.

UNII — 6P1Y2SNF5V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Trifluoperazine Hydrochloride). A white to pale yellow, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in ether. A 10% solution in water has a pH of 1.6 to 2.5. Protect from light.

USP 36: (Trifluoperazine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. Soluble 1 in 3.5 of water, 1 in 11 of alcohol, and 1 in 100 of chloroform; insoluble in ether and in benzene. pH of a 1 in 20 solution is between 1.7 and 2.6. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Trifluoperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p. 1045.3). It has a piperazine side-chain.

Trifluoperazine is used in the treatment of a variety of psychiatric disorders including schizophrenia (below), severe anxiety (p. 1028.1), and disturbed behaviour (p. 1030.2). It is also used for the control of nausea and vomiting (p. 1814.3).

Trifluoperazine is given orally as the hydrochloride but doses are expressed in terms of the base. Trifluoperazine 1 mg is equivalent to about 1.2 mg of trifluoperazine hydrochloride. A modified-release preparation is available in some countries. It has also been given by intramuscular injection. Trifluoperazine should be given in reduced dosage to elderly or debilitated patients.

The usual initial oral dose for the treatment of schizophrenia and other **psychoses** is 2 to 5 mg twice daily, gradually increased to a usual range of 15 to 20 mg daily; in severe or resistant psychoses daily doses of 40 mg or more have been given.

For the control of **nausea and vomiting** the usual oral dose is 1 or 2 mg twice daily; up to 6 mg daily may be given in divided doses.

When used as an adjunct in the short-term management of **severe anxiety disorders** doses are similar to those used for the control of nausea and vomiting.

For details of doses in children, see below.

Administration in children. The initial oral dose of trifluoperazine for the treatment of schizophrenia and other psychoses in children under 12 years old is up to 5 mg daily given in divided doses. Thereafter, the dose may be adjusted according to age, body-weight, and response, at intervals of not less than 3 days; US licensed product information suggests a usual maximum of 15 mg daily in children aged 6 to 12 years.

For the control of nausea and vomiting children aged 3 to 5 years may be given up to 1 mg daily in divided doses; this may be increased to a maximum of 4 mg daily in those aged 6 to 12 years.

When used as an adjunct in the short-term management of severe anxiety disorders doses are similar to those used for the control of nausea and vomiting.

Children and adolescents aged 12 years and over may be given usual adult doses, see above.

Schizophrenia. A systematic review[1] of the use of trifluoperazine for schizophrenia (p. 1031.3) concluded that it appeared to be of similar efficacy to other commonly used classical antipsychotics with a similar profile of adverse effects. However, there did not appear to be good evidence for claims that it was effective for schizophrenia at low doses.

1. Marques LO, *et al.* Trifluoperazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 17/05/05).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Trifluoperazine is less likely to cause sedation, hypotension, hypothermia, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects particularly when the daily dose exceeds 6 mg.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trifluoperazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Trifluoperazine hydrochloride is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1.5 to 6 hours after oral doses. Bioavailability is subject to interindividual variation. It is highly bound to plasma proteins. The elimination of trifluoperazine is multiphasic and the terminal half-life is about 22 hours. The major metabolite is the possibly active *N*-oxide. Other metabolites include the sulfoxide and the 7-hydroxy derivative. Trifluoperazine is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cuait Trifluoperazina; Stelazine; *Austral.*: Stelazine; *Braz.*: Stelazine; *Canad.*: Terfluzine†; *Gr.*: Oxyperazine; Stelazine; Stelium; *Hong Kong*: Stelazine; *India*: Gencalm; Neocalm; Trinicalm; *Indon.*: Stelazine; Stelosi; *Irl.*: Stelazine; *Ital.*: Modalina; *Mex.*: Flupazine; Stelazine; *NZ*: Stelazine; *Rus.*: Triphtazine (Трифтазин); *S. Afr.*: Stelazine; Terfluranzine†; *Spain*: Eskazine†; *Thai.*: Psyrazine; Triflumed; Triozine; Triplex†; *Turk.*: Stilizan; *UK*: Stelazine; *Venez.*: Leptazine; Taclorpil.

Multi-ingredient Preparations. *Arg.*: Cuait D; Cuait N†; Stelapar; *India*: Benzyzine; Cloxide Plus; Cynosleep; Equicalm; F Plus; Fit; Gastabid; Gencalm Plus; Kaytrix-C; Lacalm Plus; Lacalm; Librosym; Librotop; Manocalm Forte; Manocalm Plus; Neocalm Forte; Neocalm Plus; Normozin; Parazin-C; Sycot; Trinicalm Forte; Trinicalm Plus; *Ital.*: Parmodalin; *Mex.*: Stelabid.

Pharmacopoeial Preparations
BP 2014: Trifluoperazine Tablets;
USP 36: Trifluoperazine Hydrochloride Injection; Trifluoperazine Hydrochloride Syrup; Trifluoperazine Hydrochloride Tablets.

Trifluperidol *(BAN, USAN, rINN)*

McN-JR-2498; R-2498; Triflupéridol; Trifluperidoli; Trifluperidolum; Трифлуперидол.
4′-Fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone.
$C_{22}H_{23}F_4NO_2$=409.4
CAS — 749-13-3.
ATC — N05AD02.
ATC Vet — QN05AD02.
UNII — R8869Q7R8I.

Trifluperidol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trifluperidol; Triflupéridol, Chlorhydrate de; Trifluperidol, hidrocloruro de; Trifluperidoli Hydrochloridum; Трифлуперидола Гидрохлорид.
$C_{22}H_{23}F_4NO_2HCl$=445.9
CAS — 2062-77-3.
ATC — N05AD02.
ATC Vet — QN05AD02.
UNII — UIC8RB6P81.

Profile

Trifluperidol is a butyrophenone with general properties similar to those of haloperidol (p. 1077.1), and has been used as the hydrochloride in the treatment of psychoses including schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Triperidol.

Triflupromazine *(BAN, rINN)*

Fluopromazine; Triflupromazina; Triflupromazinum; Трифлупромазин.
NN-Dimethyl-3-(2-trifluoromethylphenothiazin-10-yl)propylamine.
$C_{18}H_{19}F_3N_2S$=352.4
CAS — 146-54-3.
ATC — N05AA05.
ATC Vet — QN05AA05.
UNII — RO16TQF95Y.

Pharmacopoeias. In *US*.

USP 36: (Triflupromazine). A light amber viscous oily liquid that crystallises into large irregular crystals during prolonged storage. Practically insoluble in water. Store in airtight containers. Protect from light.

Triflupromazine Hydrochloride *(BANM, rINNM)*

Fluopromazine Hydrochloride; Hidrocloruro de triflupromazina; Triflupromazina, hidrocloruro de; Triflupromazine, Chlorhydrate de; Triflupromazini Hydrochloridum; Трифлупромазина Гидрохлорид.
$C_{18}H_{19}F_3N_2S,HCl$=388.9
CAS — 1098-60-8.
ATC — N05AA05.
ATC Vet — QN05AA05.
UNII — 9E75N4A5HM.

Pharmacopoeias. In *US*.

USP 36: (Triflupromazine Hydrochloride). A white to pale tan crystalline powder having a slight characteristic odour. Soluble 1 in less than 1 of water and of alcohol and 1 in 1.7 of chloroform; soluble in acetone; insoluble in ether. Store in glass containers. Protect from light.

Profile

Triflupromazine hydrochloride is a phenothiazine with general properties similar to those of chlorpromazine (p. 1045.2). It has been used mainly in the management of psychoses and the control of nausea and vomiting. Triflupromazine hydrochloride has usually been given by injection but in some countries oral preparations may have been available.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Siquil.

Pharmacopoeial Preparations
USP 36: Triflupromazine Hydrochloride Injection; Triflupromazine Hydrochloride Tablets; Triflupromazine Oral Solution.

Trimetozine *(USAN, rINN)*

Abbott-22370; NSC-62939; PS-2383; Trimetozina; Trimétozine; Trimetozinum; Триметоцин.
4-(3,4,5-Trimethoxybenzoyl)morpholine.
$C_{14}H_{19}NO_5$=281.3
CAS — 635-41-6.
UNII — 31EPT7G9PL.

Profile

Trimetozine has been used for its sedative properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Trioxazin†.

Valnoctamide *(USAN, rINN)*

McN-X-181; NSC-32363; Valnoctamida; Valnoctamidum; Вальноктамид.
2-Ethyl-3-methylvaleramide.
$C_8H_{17}NO$=143.2
CAS — 4171-13-5.
ATC — N05CM13.
ATC Vet — QN05CM13.
UNII — 3O25NRX9YG.

Profile

Valnoctamide, an isomer of valpromide (p. 553.2), has been given orally in the treatment of anxiety disorders.

References.
1. Bialer M, *et al.* Pharmacokinetics of a valpromide isomer, valnoctamide, in healthy subjects. *Eur J Clin Pharmacol* 1990; **38**: 289–91.
2. Barel S, *et al.* Stereoselective pharmacokinetic analysis of valnoctamide in healthy subjects and in patients with epilepsy. *Clin Pharmacol Ther* 1997; **61**: 442–9.
3. Bersudsky Y, *et al.* Valnoctamide as a valproate substitute with low teratogenic potential in mania: a double-blind, controlled, add-on clinical trial. *Bipolar Disord* 2010; **12**: 376–82.

Interactions. For a discussion of the potential interaction between carbamazepine and valnoctamide, see Antiepileptics, p. 516.3.

Veralipride *(rINN)*

Veraliprida; Véralipride; Veralipridum; Верапирид.
N-[(1-Allyl-2-pyrrolidinyl)methyl]-5-sulphamoyl-2-veratramide.
$C_{17}H_{25}N_3O_5S$=383.5
CAS — 66644-81-3.
ATC — N05AL06.
ATC Vet — QN05AL06.
UNII — S7064109UD.

Profile

Veralipride is a substituted benzamide antipsychotic that has been used in the treatment of cardiovascular and psychological symptoms associated with the menopause. Preparations of veralipride have now been withdrawn from the market in some countries because of the opinion that there is an unacceptable balance of risks and benefits; adverse effects such as anxiety, depression, and tardive dyskinesia have been associated with veralipride, both during and after treatment.

Menopausal disorders. HRT with oestrogens is the mainstay of treatment for acute symptoms associated with the menopause (see p. 2245.1) but when it is considered to be unsuitable a variety of other drugs including veralipride have been tried.[1] It has also been tried with raloxifene in postmenopausal women.[2] However, treatment with veralipride has been associated with extrapyramidal adverse effects[3,4] and it has since been withdrawn from the market in some countries (see also above).

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40**: 220–30.
2. Morgante G, *et al.* Veralipride administered in combination with raloxifene decreases hot flushes and improves bone density in early postmenopausal women. *Gynecol Endocrinol* 2004; **18**: 194–8.
3. Masmoudi K, *et al.* Troubles extrapyramidaux sous véralipride (Agréa), traitement symptomatique des bouffées de chaleur: à propos de 17 c s. *Rev Med Interne* 2005; **26**: 453–7.
4. Raja M, Azzoni A. Tardive dyskinesia after long-term veralipride treatment. *J Neuropsychiatr Clin Neurosci* 2005; **17**: 252–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Veralipral; *Braz.*: Agreal; *Chile*: Agreal†; *Gr.*: Phyllan; *Mex.*: Aclimafel; Veraligral†.

Multi-ingredient Preparations. *Arg.*: Veralipral T.

Zaleplon *(BAN, USAN, rINN)*

CL-284846; L-846; LJC-10846; Tsaléploni; ZAL-846; Zaleplón Zaléplone; Zaleplonum; Залеплон.
3′-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetanilide
$C_{17}H_{15}N_5O$=305.3
CAS — 151319-34-5.
ATC — N05CF03.
ATC Vet — QN05CF03.
UNII — S62U433RMH.

Pharmacopoeias. In *US*.

USP 36: (Zaleplon). A white to off-white powder. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in propylene glycol. Protect from light.

Uses and Administration

Zaleplon is a pyrazolopyrimidine with similar sedative properties to the benzodiazepines (see Diazepam, p. 1063.3). It is used as a hypnotic in the short-term management of insomnia (below). Zaleplon has a rapid onset and short duration of action. The usual oral dose is 10 mg at bedtime although US licensed product information notes that some patients may require 20 mg. Elderly or debilitated patients or those also taking cimetidine should be given 5 mg. For dosages in patients with hepatic impairment, see below.

Administration in hepatic impairment. The oral dose of zaleplon should be reduced to 5 mg at bedtime in patients with mild to moderate hepatic impairment; it should not be given to those with severe impairment.

Insomnia. Zaleplon is a pyrazolopyrimidine hypnotic. Although not related structurally to the benzodiazepines it appears to act by binding selectively to the benzodiazepine type I receptor (BZ1- or ω_1-receptors) on the GABA subtype A complex. Zaleplon reduces sleep latency but has little effect on sleep duration; it is rapidly absorbed and eliminated and consequently residual effects the next day are said to be minimal. These characteristics make it best suited for the treatment of patients with insomnia (p. 1033.2) who have difficulty falling asleep; zaleplon can either be taken at bedtime or during the night if a patient has trouble falling back to sleep, provided they are assured of at least 4 hours uninterrupted sleep.

References.
1. Anonymous. Zaleplon for insomnia. *Med Lett Drugs Ther* 1999; **41**: 93–4.
2. Danjou P, *et al.* A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. *Br J Clin Pharmacol* 1999; **48**: 367–74.
3. Elie R, *et al.* Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry* 1999; **60**: 536–44.
4. Dooley M, Plosker GL. Zaleplon: a review of its use in the treatment of insomnia. *Drugs* 2000; **60**: 413–45.
5. George CFP. Pyrazolopyrimidines. *Lancet* 2001; **358**: 1623–6.
6. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26**: 261–82.
7. Barbera J, Shapiro [sic] C. Benefit-risk assessment of zaleplon in the treatment of insomnia. *Drug Safety* 2005; **28**: 301–18.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. Zaleplon should be used with caution and in reduced doses in patients with hepatic impairment, and should be avoided where this is severe.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to patients who present within one hour of ingestion of more than 50 mg zaleplon by adults, or 1 mg/kg by children, provided that the airway can be protected. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zaleplon toxicity.

References.
1. Israel AG, Kramer JA. Safety of zaleplon in the treatment of insomnia. *Ann Pharmacother* 2002; 36: 852–9.

Abuse. In a controlled study in healthy patients with a history of drug abuse, zaleplon was shown to have a comparable abuse potential to that of the benzodiazepine, triazolam.[1]

1. Rush CR, *et al.* Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. *Psychopharmacology (Berl)* 1999; 145: 39–51.

Breast feeding. Licensed product information for zaleplon advises that it should not be given to breast-feeding mothers since, although only a small amount is excreted into breast milk, the effect on the nursing infant is not known.

Zaleplon was detected in the breast milk of 5 women who had been given a 10-mg dose.[1] The milk-to-plasma concentration ratio for zaleplon was about 0.5. No infants were breast fed during the study.

1. Darwish M, *et al.* Rapid disappearance of zaleplon from breast milk after oral administration to lactating women. *J Clin Pharmacol* 1999; 39: 670–4.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zaleplon, see under Zolpidem, p. 1117.2.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zaleplon, see under Zolpidem, p. 1117.2.

Overdosage. A report of overdose with zaleplon noted for the blue-green discoloration of the patient's mouth and lips, urine, and emesis, which was attributed to the dye used in the zaleplon capsules ingested.[1]

1. Louis CJ, *et al.* A case of zaleplon overdose. *Clin Toxicol* 2008; 46: 782.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zaleplon as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1. Zaleplon is primarily metabolised by aldehyde oxidase and use with inhibitors of this enzyme, such as cimetidine, may result in increased plasma concentrations of zaleplon (see Uses and Administration, p. 1114.3). Zaleplon is also partly metabolised by the cytochrome P450 isoenzyme CYP3A4 and, consequently, caution is advised when zaleplon is given with drugs that are substrates for, or potent inhibitors of, this isoenzyme. Cimetidine is also an inhibitor of CYP3A4 and thus inhibits both the primary and secondary metabolic pathways of zaleplon.

Use with rifampicin or other potent enzyme-inducing drugs may accelerate the metabolism of zaleplon and reduce its plasma concentrations.

Pharmacokinetics

Zaleplon is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in about one hour after oral dosage. A heavy meal or one with a high-fat content delays absorption and reduces peak concentrations. Bioavailability is about 30% due to significant first-pass hepatic metabolism. Zaleplon is metabolised primarily by aldehyde oxidase to form 5-oxo-zaleplon and, to a lesser extent, by the cytochrome P450 isoenzyme CYP3A4 to desethylzaleplon, which is further metabolised by aldehyde oxidase to 5-oxo-desethylzaleplon. The plasma-elimination half-life of zaleplon is about 1 hour. About 70% of a dose is excreted in the urine as these inactive metabolites or their glucuronides; less than 1% is excreted unchanged. About 17% of a dose is eliminated in the faeces, mainly as 5-oxo-zaleplon. Zaleplon is distributed into breast milk.

References.
1. Greenblatt DJ, *et al.* Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. *Clin Pharmacol Ther* 1998; 64: 553–61.
2. Drover D, *et al.* Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; 22: 1443–61.
3. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; 43: 227–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hegon; Hipnodem; *Belg.*: Sonata; *Braz.*: Sonata; *Chile*: Plenidon; Sedartryl; *China*: An Ji Xin (安己辛); An Wei De (安维得); An Yun (安云); Bai Jie Min (百介民); En Nuo Xin (恩诺欣); He Bang Li An (禾邦立安); Hui Ning (惠宁); Hui Te Ning (惠特宁); Qu Ning (曲宁); Rui Chen (瑞晨); Si Mei (思每); Si Te Chang Jia (斯特长佳); Siweitan (思威坦); Tong An Qi (通安其); *Cz.*: Sonata; Zerene; *Denm.*: Sonata; *Fin.*: Sonata†; *Ger.*: Sonata; *Gr.*: Sonata; *Hung.*: Sonata; *India*: Zalep; Zaplon; Zaso; *Irl.*: Sonata; Zerene; *Ital.*: Sonata; Zerene†; *Neth.*: Sonata; Zerene†; *Pol.*: Selofen; Sonata; Zerene; *Port.*: Sonata; Zerene; *Rus.*: Andante (Андante); *Spain*: Sonata†; *Swed.*: Sonata; *Switz.*: Sonata; *UK*: Sonata; *Ukr.*: Andante (Анданте); Selofen (Селофен); *USA*: Sonata.

Pharmacopoeial Preparations
USP 36: Zaleplon Capsules.

Ziprasidone *(BAN, rINN)*

Ziprasidona; Ziprasidonum; Зипрасидон.
5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone.
$C_{21}H_{21}ClN_4OS$=412.9
CAS — 146939-27-7 (ziprasidone).
ATC — N05AE04.
ATC Vet — QN05AE04.
UNII — 6UKA5VEJ6X.

Ziprasidone Hydrochloride

(BANM, USAN, rINNM)

CP-88059-1; CP-88059; Hidrocloruro de ziprasidona; Ziprasidona, hidrocloruro de; Ziprasidone, Chlorhydrate de; Ziprasidoni hydrochloridum; Зипрасидона Гидрохлорид.
$C_{21}H_{21}ClN_4OS,HCl,H_2O$=467.4
CAS — 122883-93-6 (anhydrous ziprasidone hydrochloride); 138982-67-9 (ziprasidone hydrochloride monohydrate).
ATC — N05AE04.
ATC Vet — QN05AE04.
UNII — 216X081ORU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ziprasidone Hydrochloride Monohydrate). A white or slightly pink powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in methyl alcohol and in dichloromethane. Protect from light.

USP 36: (Ziprasidone Hydrochloride). A white to slightly pink powder. Practically insoluble in water; very soluble in methyl alcohol; slightly soluble in isopropyl alcohol and in hot tetrahydrofuran. Store in airtight containers. Protect from light.

Ziprasidone Mesilate *(BANM, rINNM)*

CP-88059/27; Mesilato de ziprasidona; Ziprasidona, mesilato de; Ziprasidone, Mésilate de; Ziprasidone Mesylate; Ziprasidoné Mesylate (USAN); Ziprasidoni Mesilas; Зипрасидона Мезилат.
$C_{21}H_{21}ClN_4OS,CH_4O_3S,3H_2O$=563.1
CAS — 199191-69-0.
ATC — N05AE04.
ATC Vet — QN05AE04.
UNII — 3X6SAX83JZ.

Uses and Administration

Ziprasidone is an atypical antipsychotic reported to have affinity for adrenergic (α_1), histamine (H_1), and serotonin (5-HT_2) receptors as well as dopamine (D_2) receptors. It is used for the treatment of schizophrenia (below) and in acute manic or mixed episodes associated with bipolar disorder (below). Ziprasidone is given orally, usually as the hydrochloride; it is also given parenterally as the mesilate. Ziprasidone bisulfate has also been used. Doses are expressed in terms of the base; ziprasidone hydrochloride 11.3 mg or ziprasidone mesilate 13.6 mg are each equivalent to about 10 mg of ziprasidone.

For the treatment of **schizophrenia**, ziprasidone hydrochloride is given in an initial oral dose equivalent to 20 mg twice daily with food. Doses may be increased if necessary at intervals of not less than 2 days up to 80 mg twice daily. For maintenance, doses as low as 20 mg twice daily may be effective.

For acute agitation in patients with schizophrenia, ziprasidone may be given as the mesilate by intramuscular injection. The recommended dose is equivalent to 10 to 20 mg as required, to a maximum of 40 mg daily for 3 consecutive days. Doses of 10 mg may be given every 2 hours and doses of 20 mg may be given every 4 hours. Patients should be switched to oral therapy as soon as possible.

For the treatment of *acute mixed or manic episodes* in **bipolar disorder**, ziprasidone hydrochloride is given in an initial oral dose equivalent to 40 mg twice daily with food. The dose should be increased to 60 or 80 mg twice daily on the second day of treatment and subsequently adjusted according to tolerance. It is also used for the *maintenance treatment* of bipolar disorder as an adjunct to lithium or valproate; patients should be continued on the same dose on which they were stabilised, within a range of 40 to 80 mg twice daily.

Bipolar disorder. Ziprasidone is effective in the management of acute mania in patients with bipolar disorder[1,2] (p. 397.2) but it may be associated with the induction of mania or hypomania in such patients.[3] It is also used as an adjunct in maintenance treatment.[4]

1. Keck PE, *et al.* Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003; 160: 741–8.
2. Keck PE, *et al.* Long-term safety and efficacy of ziprasidone in subpopulations of patients with bipolar mania. *J Clin Psychiatry* 2009; 70: 844–51.
3. Baldassano CF, *et al.* Ziprasidone-associated mania: a case series and review of the mechanism. *Bipolar Disord* 2003; 5: 72–5.
4. Bowden CL, *et al.* Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 2010; 71: 130–7.

Schizophrenia. A systematic review[1] of the efficacy and safety of ziprasidone in patients with schizophrenia (p. 1031.3) found that from the limited data available ziprasidone was as effective as haloperidol; it was less likely to provoke extrapyramidal disorders but appeared to cause more nausea and vomiting, and pain at the site of injection. A comparative study[2] of intramuscular ziprasidone with intramuscular haloperidol also found a favourable outcome in patients with acute psychoses. At the time comparisons with other atypical antipsychotics were lacking. However, a more recent review,[3] concluded that, based on limited data, ziprasidone may be slightly less effective than amisulpride, olanzapine, and risperidone but had a lower propensity to induce weight gain and associated adverse effects.

1. Bagnall A, *et al.* Ziprasidone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 20/10/05).
2. Brook S, *et al.* Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; 61: 933–41.
3. Komossa K, *et al.* Ziprasidone versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 23/11/09).

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p. 1030.1), haloperidol or pimozide are commonly used but atypical antipsychotics such as ziprasidone are increasingly being tried.[1]

1. Sallee FR, *et al.* Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000; 39: 292–9.

Adverse Effects, Treatment, and Precautions

Although ziprasidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p. 1047.2), the incidence and severity of such effects may vary. Frequent adverse effects with ziprasidone include somnolence, rash or urticaria, gastrointestinal disturbances, dizziness, flu-like symptoms, hypertension, headache, agitation, confusion, and dyspnoea. Orthostatic hypotension may be a problem, particularly when starting treatment. Ziprasidone may increase prolactin levels and weight gain has also been noted. Sexual dysfunction has been reported infrequently. Extrapyramidal symptoms may occur, and tardive dyskinesia may develop with prolonged use. There have also been infrequent or rare cases of cholestatic jaundice, hepatitis, seizures, blood dyscrasias including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia, and hyperlipidaemia. Hyperglycaemia occurs uncommonly with ziprasidone. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of, developing diabetes.

Ziprasidone has been associated with dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use is contra-indicated in patients with a history of QT prolongation or cardiac arrhythmias, with recent acute myocardial infarction, or with decompensated heart failure. Certain medications may also increase the risk (see Interactions, p. 1116.1). Baseline serum potassium and magnesium screening should be performed in patients who are at risk of significant electrolyte disturbances and hypokalaemia or hypomagnesaemia should be corrected before starting ziprasidone therapy. Serum electrolytes should be monitored in patients who start diuretic therapy during ziprasidone treatment. Patients receiving ziprasidone who have symptoms that might indicate torsade de pointes

(e.g. dizziness, palpitations, or syncope) should be further evaluated.

Ziprasidone should be used with caution in patients with a history of seizures or in conditions that lower the seizure threshold, cardiovascular or cerebrovascular disease, or conditions which predispose to hypotension. Since intramuscular injections are formulated with cyclodextrin, which is cleared by renal filtration, licensed product information recommends caution in patients with renal impairment.

Ziprasidone may affect the performance of skilled tasks including driving.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p. 1059.1.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p. 1059.2.

Effects on the cardiovascular system. For a discussion of sudden unexpected deaths associated with antipsychotic use, see under Adverse Effects of Chlorpromazine, p. 1047.3.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p. 1049.1. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p. 1059.2.

The elderly. For a discussion of the risks associated with antipsychotic use in the elderly, see under Precautions of Chlorpromazine, p. 1051.1. The use of atypical antipsychotics in elderly patients with **dementia** is also discussed in further detail under Risperidone, p. 1105.1.

Extrapyramidal disorders. Tardive dyskinesia has been associated with ziprasidone therapy;[1-3] onset ranged from 2 to 34 months after starting the drug. Acute dystonia has also been reported[4,5] with ziprasidone. However, the incidence of extrapyramidal adverse effects (p. 1049.2) is generally lower with atypical than classical antipsychotics.

1. Rosenquist KJ, *et al.* Tardive dyskinesia and ziprasidone. *Am J Psychiatry* 2002; **159**: 1436.
2. Keck ME, *et al.* Ziprasidone-related tardive dyskinesia. *Am J Psychiatry* 2004; **161**: 175–6.
3. Ananth J, *et al.* Tardive dyskinesia in 2 patients treated with ziprasidone. *J Psychiatry Neurosci* 2004; **29**: 467–9.
4. Ziegenbein M, *et al.* Ziprasidone-induced Pisa syndrome after clozapine treatment. *J Neuropsychiatr Clin Neurosci* 2003; **15**: 458–9.
5. Mason MN, *et al.* Ziprasidone-induced acute dystonia. *Am J Psychiatry* 2005; **162**: 625–6.

Mania. Although it is used in the treatment of bipolar disorder, ziprasidone has been associated with reports of mania in bipolar patients, see under Uses and Administration, p. 1115.3.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS—p. 1050.2) has been associated with ziprasidone;[1] however, the patient had also received lithium, a drug that has been associated with NMS.

1. Borovicka MC, *et al.* Ziprasidone- and lithium-induced neuroleptic malignant syndrome. *Ann Pharmacother* 2006; **40**: 139–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ziprasidone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For comments on the use of some atypical antipsychotics, including ziprasidone, during pregnancy, see under Precautions of Clozapine, p. 1061.2.

US licensed product information states that ziprasidone showed possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Ziprasidone should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

Use of ziprasidone with other drugs known to prolong the QT interval is contra-indicated because of the increased risk of arrhythmias. Monitoring of serum electrolytes is recommended if ziprasidone is given with diuretics.

The metabolism of ziprasidone is mediated by the cytochrome P450 isoenzyme CYP3A4. Therefore, there is the potential for interactions between ziprasidone and other drugs that induce, inhibit, or act as a substrate for this enzyme.

Ziprasidone may enhance the effects of other CNS depressants and certain antihypertensives; it may antagonise the effects of levodopa and dopaminergics.

Pharmacokinetics

Ziprasidone is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 6 to 8 hours after oral doses. The presence of food may double the absorption. After intramuscular injection, peak plasma concentrations occur within 1 hour. Plasma protein binding is about 99%. Ziprasidone is extensively metabolised by aldehyde oxidase (about 66% of a dose) and by the cytochrome P450 isoenzyme CYP3A4. The mean terminal elimination half-life has been reported to be about 7 hours after oral dosage and about 2 to 5 hours after intramuscular dosage. Ziprasidone is excreted mainly as metabolites in the faeces (about 66%) and urine (about 20%); less than 5% of a dose appears as unchanged drug.

References.
1. Various. The pharmacokinetics of ziprasidone. *Br J Clin Pharmacol* 2000; **49** (suppl 1): 1S–76S.
2. Miceli JJ, *et al.* Pharmacokinetics, safety, and tolerability of intramuscular ziprasidone in healthy volunteers. *J Clin Pharmacol* 2005; **45**: 620–30.
3. Preskorn SH. Pharmacokinetics and therapeutics of acute intramuscular ziprasidone. *Clin Pharmacokinet* 2005; **44**: 1117–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zeldox; *Austral.*: Zeldox; *Austria*: Zeldox; *Braz.*: Geodon; *Canad.*: Zeldox; *Chile*: Zeldox; *China*: Li Fu Jun An (力复君安); Si Bei Ge (思贝格); Zeldox (卓乐定); *Cz.*: Zeldox; Zipsi; Zypsila; *Denm.*: Geodon; Zeldox; *Fin.*: Zeldox; *Ger.*: Zeldox; *Gr.*: Geodon; *Hong Kong*: Zeldox; *Hung.*: Ypsila; Zeldox; *India*: Azona; Zipsydon; *Irl.*: Geodon; *Israel*: Geodon; *Ital.*: Zeldox; *Malaysia*: Zeldox; *Mex.*: Geodon; *Norw.*: Zeldox; *NZ*: Zeldox; *Philipp.*: Zeldox†; *Pol.*: Pramaxima; Zeldox; Zipragen; Zipwell; Zypsila; *Port.*: Zeldox; *Rus.*: Zeldox (Зелдокс); *S.Afr.*: Geodon; *Singapore*: Zeldox; *Spain*: Geodon; Zeldox; Zypsilan; *Swed.*: Zeldox; *Thai.*: Zeldox; *Turk.*: Zeldox; *Ukr.*: Zeldox (Зелдокс); *USA*: Geodon; *Venez.*: Geodon.

Zolazepam Hydrochloride

(BANM, USAN, rINNM)

CI-716; Hidrocloruro de zolazepam; Zolazépam, Chlorhydrate de; Zolazepam, hidrocloruro de; Zolazepami Hydrochloridum; Золазепама Гидрохлорид.

4-(o-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpirazole[3,4-e][1,4]diazepin-7(1*H*)-one monohydrochloride.

$C_{15}H_{15}FN_4O.HCl$=322.8

CAS — 31352-82-6 (zolazepam); 33754-49-3 (zolazepam hydrochloride).

UNII — 45SJ093Q1N.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Zolazepam Hydrochloride). A white to off-white crystalline powder. Freely soluble in water and in 0.1N hydrochloric acid; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. pH of a 10% solution in water is between 1.5 and 3.5. Store in airtight containers.

Profile

Zolazepam hydrochloride is a benzodiazepine with general properties similar to those of diazepam (p. 1063.2). It is used with tiletamine (p. 1920.1) for general anaesthesia in veterinary medicine.

Zolpidem Tartrate *(BANM, USAN, rINNM)*

SL-80.0750-23N; SL-80.0750 (zolpidem); Tartrato de zolpidem; Tsolpideemitartraatti; Zolpidem Hemitartrate; Zolpidem, tartrate de; Zolpidem, tartrato de; Zolpidemi Tartras; Zolpidemo tartratas; Zolpidem-tartarát; Zolpidemtartrat; Zolpidemu winian; Золпидема Тартрат.

N,N-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide hemitartrate.

$(C_{19}H_{21}N_3O)_2.C_4H_6O_6$=764.9

CAS — 82626-48-0 (zolpidem); 99294-93-6 (zolpidem tartrate).

ATC — N05CF02.

ATC Vet — QN05CF02.

UNII — WY6W63843K.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of zolpidem tartrate:

Sleepeasy; Tic-Tacs.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Zolpidem Tartrate). A white or almost white hygroscopic crystalline powder. Slightly soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Zolpidem Tartrate). White to off-white, hygroscopic powder. Slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines (see Diazepam, p. 1063.3), but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and is used as a hypnotic in the short-term management of insomnia (below), including when waking in the middle of the night is followed by difficulty returning to sleep.

The usual oral or sublingual dose in patients who have difficulty in falling to sleep is 10 mg taken immediately before retiring; however, some licensed product information recommend an initial dose of 5 mg, particularly for women because of reduced zolpidem clearance (for details see Pharmacokinetics, p. 1117.3). In elderly or debilitated patients, treatment should be limited to a dose of 5 mg at night.

In the treatment of difficulty returning to sleep after waking in the middle of the night, zolpidem tartrate may be taken sublingually provided there are more than 4 hours of planned sleep remaining. The usual dose is 1.75 mg for women and 3.5 mg for men; elderly patients should be given 1.75 mg regardless of gender.

Doses should also be reduced in patients with hepatic impairment, see below.

Modified-release and oral spray formulations of zolpidem tartrate are also available.

Administration in hepatic impairment. For the treatment of insomnia in patients with hepatic impairment who have difficulty in falling asleep, zolpidem tartrate should be started at an oral or sublingual dose of 5 mg at bedtime regardless of gender; this may be increased to 10 mg, if necessary, in those aged under 65 years. UK licensed product information contra-indicates the use of zolpidem in patients with severe impairment.

In the treatment of difficulty returning to sleep after waking in the middle of the night, zolpidem tartrate may be given sublingually at a dose of 1.75 mg regardless of gender provided there are more than 4 hours of planned sleep remaining.

Catatonia. Anecdotal reports[1,2] suggesting that zolpidem may be a useful test in the diagnosis of catatonia.

1. Thomas P, *et al.* Test for catatonia with zolpidem. *Lancet* 1997; **349**: 702.
2. Zaw ZF, Bates GDL. Replication of zolpidem test for catatonia in an adolescent. *Lancet* 1997; **349**: 1914.

Insomnia. Zolpidem is an imidazopyridine with strong sedative actions, but only minor anxiolytic, muscle relaxant, or anticonvulsant properties. Some degree of amnesia has been reported. Zolpidem appears to act by binding to the benzodiazepine receptor component of the GABA receptor complex. It has, however, a selective affinity for the subtype of benzodiazepine receptors prevalent in the cerebellum (BZ1-or ω_1-receptors) as opposed to those more commonly found in the spinal cord (BZ2- or ω_2-receptors) or in the peripheral tissues (BZ3-or ω_3-receptors). Zolpidem has a rapid onset and short duration of hypnotic action and at usual doses decreases time to sleep onset and increases duration of sleep with little apparent effect on sleep stages (see Insomnia, p. 1033.2). Reviews agree that clinical studies have shown zolpidem to have hypnotic activity superior to placebo and generally similar to comparative benzodiazepines. Although it does not appear to produce rebound insomnia to any great extent, there appears to be little evidence that zolpidem offers any advantage over short-acting benzodiazepines in terms of residual effects the next day, or its potential to induce tolerance or withdrawal symptoms or dependence (see also under Dependence and Withdrawal, p. 1117.1).

References.
1. Langtry HD, Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 1990; **40**: 291–313.
2. Lobo BL, Greene WL. Zolpidem: distinct from triazolam? *Ann Pharmacother* 1997; **31**: 625–32.
3. Nowell PD, *et al.* Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA* 1997; **278**: 2170–7.
4. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000; **59**: 865–89.
5. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26**: 261–82.

6. Harrison TS, Keating GM. Zolpidem: a review of its use in the management of insomnia. *CNS Drugs* 2005; 19: 65–89.
7. Moen MD, Plosker GL. Zolpidem extended-release. *CNS Drugs* 2006; 20: 419–26.
8. Barkin RL. Zolpidem extended-release: a single insomnia treatment option for sleep induction and sleep maintenance symptoms. *Am J Ther* 2007; 14: 299–305.
9. Yang LP, Deeks ED. Sublingual zolpidem (Edluar®; Sublinox®). *CNS Drugs* 2012; 26: 1003–10.
10. Roth T, *et al.* Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. *Sleep* 2013; 36: 189–96.

Parkinsonism. Although preliminary findings[1] in 10 patients suggested that zolpidem might improve symptoms of Parkinson's disease concern has been expressed[2] over the risk of falls associated with zolpidem-induced drowsiness and the serious consequences for these patients. Benefit has also been reported[3] in the treatment of antipsychotic-induced parkinsonism in one patient with symptoms of repetitive persistent gross tremors of the hands.

1. Daniele A, *et al.* Zolpidem in Parkinson's disease. *Lancet* 1997; 349: 1222–3.
2. Lavoisy J, Marsac J. Zolpidem in Parkinson's disease. *Lancet* 1997; 350: 74.
3. Farver DK, Khan MH. Zolpidem for antipsychotic-induced parkinsonism. *Ann Pharmacother* 2001; 35: 435–7.

Permanent vegetative state. Zolpidem in a single dose of 10 mg has produced temporary arousal in 3 patients thought to be in permanent vegetative state.[1] Effects lasted for about 4 hours.

1. Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation* 2006; 21: 23–8.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

Withdrawal symptoms. A 37-year-old man, who increased his dose from 10 mg to 130 mg daily over 2 months, had a generalised tonic-clonic seizure after zolpidem was abruptly stopped.[1] The patient recovered after being started on a benzodiazepine dosage tapering programme. Symptoms attributed to daytime abstinence after excessive night-time doses have been reported[2] in 2 patients and included anxiety, tremor, sweating, nausea, gastric and abdominal pain, swallowing difficulties, tachycardia, and tachypnoea. The patients had increased their doses because of the development of tolerance to the hypnotic effect but had begun to have muscle twitches and myoclonic jerks.

1. Gilbert DL, Staats PS. Seizure after withdrawal from supratherapeutic doses of zolpidem tartrate, a selective omega 1 benzodiazepine receptor agonist. *J Pain Symptom Manage* 1997; 14: 118–20.
2. Cavallaro R, *et al.* Tolerance and withdrawal with zolpidem. *Lancet* 1993; 342: 374–5.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to adults or children who present within one hour of ingesting more than 1 mg/kg of zolpidem. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zolpidem toxicity (but see also Overdosage, below).

Reviews.

1. Darcourt G, *et al.* The safety and tolerability of zolpidem—an update. *J Psychopharmacol* 1999; 13: 81–93.

Abuse. Zolpidem abuse has been reported;[1,2] effects noted include a paradoxical stimulant effect when taking large doses. Tolerance may also develop. Intravenous abuse has also been reported.[3]

See also Withdrawal Symptoms, above.

1. Gericke CA, Ludolph AC. Chronic abuse of zolpidem. *JAMA* 1994; 272: 1721–2.
2. Victorri-Vigneau C, *et al.* Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol* 2007; 64: 198–209.
3. Brunelle E, *et al.* Zolpidem: intravenous misuse in drug abusers. *Addiction* 2005; 100: 1377–8.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving zolpidem, and the *American Academy of Pediatrics considers*[1] that it is therefore usually compatible with breast feeding.

In 5 women given a 20-mg dose of zolpidem, the amount of drug excreted in breast milk after 3 hours ranged between 0.76 and 3.88 micrograms, which represented 0.004 to 0.019% of the dose.[2] No detectable (below 0.5 nanograms/mL) zolpidem was found in subsequent milk samples.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)
2. Pons G, *et al.* Zolpidem excretion in breast milk. *Eur J Clin Pharmacol* 1989; 37: 245–8.

Effects on the liver. Hepatitis developed on 2 separate occasions in a 53-year-old woman after the use of zolpidem for insomnia.[1]

1. Karsenti D, *et al.* Hepatotoxicity associated with zolpidem treatment. *BMJ* 1999; 318: 1179.

Effects on mental function. Psychotic reactions, which may not subsequently be recalled, have been reported in patients taking therapeutic doses of zolpidem.[1–4] Somnambulism has also been reported with zolpidem.[5,6] Other complex sleep-related behaviours, such as eating or driving while asleep, have been reported with zaleplon,[7] zolpidem,[6,7] and zopiclone. Such behaviour is more likely to occur when these drugs are taken with alcohol or other CNS depressants, or when taken in doses exceeding the recommended maximum. It is not clear if there are differences in risk with individual drugs; however, as a precautionary measure, the FDA[8] had requested for labelling changes that highlight these adverse effects to be made to all hypnotics marketed in the USA. There has also been a report of a patient who took 40 mg of zolpidem orally and stabbed himself after being commanded by the resulting auditory hallucinations to do so.[9]

1. Ansseau M, *et al.* Psychotic reactions to zolpidem. *Lancet* 1992; 339: 809.
2. Iruela LM, *et al.* Zolpidem-induced macropsia in anorexic woman. *Lancet* 1993; 342: 443–4.
3. Brodeur MR, Stirling AL. Delirium associated with zolpidem. *Ann Pharmacother* 2001; 35: 1562–4.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Seeing things with zolpidem. *Aust Adverse Drug React Bull* 2002; 21: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0202.pdf (accessed 21/08/08)
5. Yang W, *et al.* One rare side effect of zolpidem—sleepwalking: a case report. *Arch Phys Med Rehabil* 2005; 86: 1265–6.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Zolpidem and bizarre sleep related effects. *Aust Adverse Drug React Bull* 2007; 26: 2–3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0702.pdf (accessed 10/03/08)
7. Southworth MR, *et al.* FDA. Nonbenzodiazepine hypnotic use and cases of "sleep driving". *Ann Intern Med* 2008; 148: 486–7.
8. FDA. FDA news: FDA requests label change for all sleep disorder drug products (issued 14th March, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108868.htm (accessed 26/07/10)
9. Manfredi G, *et al.* Command hallucinations with self-stabbing associated with zolpidem overdose. *J Clin Psychiatry* 2010; 71: 92–3.

Hypersensitivity. Rare cases of angioedema involving the tongue, glottis, or larynx have been reported after the first or subsequent doses of hypnotics such as eszopiclone, zaleplon, zolpidem, and zopiclone; additional symptoms suggestive of anaphylaxis have also developed in some patients.

Overdosage. A retrospective analysis of 344 cases of acute overdosage with zolpidem reported to the Paris Poison Center and the manufacturers *Synthelabo* has been published.[1] The ingested dose, where known, ranged from 10 to 1400 mg, and the most common adverse effect was drowsiness (in 89 patients). Other adverse effects probably associated with the overdosage included coma in 4 patients and vomiting in 7. Recovery was usually rapid when overdosage involved only zolpidem. The authors recommended that patients who had ingested more than 100 mg of zolpidem should undergo gastric lavage and should be monitored for at least 12 hours (but see Adverse Effects, Treatment, and Precautions, above). Although flumazenil (p. 1552.2) may be used to reverse the effects of zolpidem toxicity, the authors of this analysis[1] found that in general it was not required.

1. Garnier R, *et al.* Acute zolpidem poisoning—analysis of 344 cases. *J Toxicol Clin Toxicol* 1994; 32: 391–404.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zolpidem as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1.

Antidepressants. A 16-year-old girl who had been taking *paroxetine* 20 mg daily for 3 days began to hallucinate and became disorientated one hour after taking zolpidem 10 mg at night. The delirium cleared spontaneously 4 hours later without treatment.[1] When questioned, at least one other of the author's patients given this combination reported transient visual hallucinations. Other isolated cases of visual hallucinations have been reported in patients taking zolpidem with antidepressants including *bupropion, desipramine, fluoxetine, sertraline,* and *venlafaxine*.[2]

1. Katz SE. Possible paroxetine-zolpidem interaction. *Am J Psychiatry* 1995; 152: 1689.
2. Elko CJ, *et al.* Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *J Toxicol Clin Toxicol* 1998; 36: 195–203.

Antiepileptics. A 47-year-old man with a history of bipolar disorder, who was receiving citalopram and zolpidem, had episodes of somnambulism after he was also given *valproic acid* for treatment of manic symptoms.[1] The episodes stopped on withdrawal of valproic acid and returned on rechallenge. An interaction between zolpidem and valproic acid was suspected (but somnambulism has also been associated with zolpidem alone, see Effects on Mental Function, above).

For the suggestion that *carbamazepine* and *phenytoin* may interact with zolpidem, see Rifampicin, below.

1. Sattar SP, *et al.* Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* 2003; 37: 1429–33.

Antifungals. Use of *ketoconazole* with zolpidem has resulted in increased plasma concentrations, and an enhanced sedative effect, of zolpidem, albeit only modest.[1] The use of zolpidem with *fluconazole*[1] or *itraconazole*[1,2] has resulted in small, non-significant changes in the pharmacokinetics and sedative effects of zolpidem.

1. Greenblatt DJ, *et al.* Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. *Clin Pharmacol Ther* 1998; 64: 661–71.
2. Luurila H, *et al.* Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. *Eur J Clin Pharmacol* 1998; 54: 163–6.

Antivirals. HIV-protease inhibitors such as *ritonavir* may increase plasma concentrations of zolpidem with a risk of extreme sedation and respiratory depression; use together is possible provided the patient is carefully monitored for excessive sedative effects.

Rifampicin. Rifampicin reduced the hypnotic effect of zolpidem in a study in 8 healthy female subjects.[1] The area under the curve for zolpidem was reduced by 73% after rifampicin and the peak plasma concentration by 58%. The elimination half-life of zolpidem was reduced from 2.5 to 1.6 hours. Similar effects could be expected with other potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as carbamazepine and phenytoin.

1. Villikka K, *et al.* Rifampin reduces plasma concentrations and effects of zolpidem. *Clin Pharmacol Ther* 1997; 62: 629–34.

Pharmacokinetics

Zolpidem is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur within 3 hours and are about 45% higher in women than in men given the same oral dose because of lower clearance rate in women. Zolpidem undergoes first-pass metabolism and an absolute bioavailability of about 70% has been reported. Zolpidem has an elimination half-life of about 2.5 hours and is about 92% bound to plasma proteins. It is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4; the inactive metabolites of zolpidem are excreted in the urine and faeces. Zolpidem is distributed into breast milk.

References.

1. Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. *Clin Pharmacokinet* 1995; 29: 142–53.
2. von Moltke LL, *et al.* Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and in vivo correlations. *Br J Clin Pharmacol* 1999; 48: 89–97.
3. Drover D, *et al.* Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; 22: 1443–61.
4. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; 43: 227–38.
5. Greenblatt DJ, *et al.* Dynamics and kinetics of a modified-release formulation of zolpidem: comparison with immediate-release standard zolpidem and placebo. *J Clin Pharmacol* 2006; 46: 1469–80.
6. Greenblatt DJ, *et al.* Comparison of pharmacokinetic profiles of zolpidem buffered sublingual tablet and zolpidem oral immediate-release tablet: results from a single-center, single-dose, randomized, open-label crossover study in healthy adults. *Clin Ther* 2013; 35: 604–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ambien; Dormilan; Durnit; Nocte; Somit; Somnipax; Sumenan; Zolodorm; ***Austral.***: Dormizol; Somidem; Stildem; Stilnox; Zolpibell†; ***Austria***: Ivadal; Mondeal; Zoldem; ***Belg.***: Stilnoct; Zolpitop; ***Braz.***: Lloram; Noctiden; Stilnox; Zylinox; ***Canad.***: Sublinox; ***Chile***: Adormix†; Damixan; Dormilam; Dormosol; Somnil; Somnipron; Somno; Stilnox; Sucedal; ***China***: Le Tan (乐坦); Nuo Bin (诺宾); Stilnox (思诺思); ***Cz.***: Eanox; Hypnogen; Insom; Stilnoct†; Stilnox; Zolpimerck†; Zolpinox; Zolsana; Zonadin†; ***Denm.***: Nimadorm†; Stilnoct; Zonoct; ***Fin.***: Somnor; Stella; Stilnoct; ***Fr.***: Stilnox; ***Ger.***: Bikalm†; Stilnox; Zoldem†; Zolpi-Lich†; Zolpi-Q†; Zolpinox; ***Gr.***: Alespan; Hypnoforin; Hypnonorm; Stilnox; ***Hong Kong***: Stilnox; Stilpidem; Vicknox; ***Hung.***: Ambien†; Hypnogen; Pidezol; Sanval; Somnogen; Stilnox; ***India***: Ambiz†; Ambulax-Z; Dactive; Dem; Inzofresh; Isodem; Nidra; Nitrest; Olpitric; Sove; Zleep; Zoldem; ***Indon.***: Stilnox; Zolmia; ***Irl.***: Nytamel; Stilnoct; Zoldem; Zolnod; ***Israel***: Ambien; Stilnox; Zodorm; ***Ital.***: Nottem; Stilnox; ***Jpn***: Myslee; ***Malaysia***: Sobrium; Somidem; Stilnox; Zopim; ***Mex.***: Nitrest; Nocte; Stil-

The symbol † denotes a preparation no longer actively marketed

nox; *Neth.*: Stilnoct; *Norw.*: Stilnoct; *Philipp.*: Stilnox; Ziohex; Zoldem; Zolpid; *Pol.*: Apo-Zolpin; Hypnogen; Nasen; Onirex; Polsen; Sanval; Stilnox; Xentic; Zolpic; ZolpiGen; Zolsana; Zoratio; *Port.*: Cymerion; Stilnox; *Rus.*: Hypnogen (Гипноген); Ivadal (Ивадал); Nitrest (Нитрест); Sanval (Санвал); Snovitel (Сновител); Zolsana (Зольсана); Zonadine (Зонадин); *S.Afr.*: Ivedal; Noxidem; Stilnox; Zolnoxs; Zolpihexal; *Singapore*: Stilnox; *Spain*: Dalparan; Stilnox; *Swed.*: Stilnoct; *Switz.*: Dorlotil; Stilnox; Zoldorm; *Thai.*: Stilnox; *UK*: Stilnoct; *USA*: Ambien; Edluar; Intermezzo; Tovalt†; Zolpimist; *Venez.*: Atrimon; Stilnox; Zolpidex.

Pharmacopoeial Preparations

USP 36: Zolpidem Tartrate Extended-Release Tablets; Zolpidem Tartrate Tablets.

Zopiclone (BAN, rINN)

27267-RP; Tsopiklon; Zopiclon; Zopiclona; Zopiclonum; Zopiklon; Zopiklonas; Зопиклон.

6-(5-Chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

$C_{17}H_{17}ClN_6O_3$=388.8

CAS — 43200-80-2.

ATC — N05CF01.

ATC Vet — QN05CF01.

UNII — 03A5ORL08Q.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of zopiclone: Zoppies.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Zopiclone). A white or slightly yellowish powder. Practically insoluble in water and in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Uses and Administration

Zopiclone is a cyclopyrrolone with similar sedative, anxiolytic, muscle relaxant, amnestic, and anticonvulsant properties to those of the benzodiazepines (see Diazepam, p. 1063.3). Like diazepam, its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA) in the brain. Zopiclone is reported to bind to the benzodiazepine receptor component of the GABA receptor complex but at a different site to the benzodiazepines. It has a short duration of action.

Zopiclone is used as a hypnotic in the short-term management of insomnia (below). The usual oral dose is 7.5 mg taken shortly before retiring. Treatment should start with a dose of 3.75 mg in elderly patients. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Eszopiclone, the (+)-isomer of zopiclone, is used similarly (see p. 1072.3).

Administration in hepatic or renal impairment. In those with renal impairment or mild to moderate hepatic impairment, treatment with zopiclone should start with an oral dose of 3.75 mg taken shortly before retiring. It should not be given to patients with severe hepatic impairment.

Insomnia. Zopiclone has a similar pharmacological and pharmacokinetic profile to the short-acting benzodiazepines. It is claimed to initiate sleep rapidly, without reduction of total rapid-eye-movement (REM) sleep, and then sustain it with preservation of normal slow-wave sleep (see Insomnia, p. 1033.2). It is generally considered to be as effective as a hypnotic as the benzodiazepines. Rebound insomnia has occurred but does not appear to be common. Residual effects the next day may be less pronounced after zopiclone than after short-acting benzodiazepines but there appears to be little evidence that zopiclone offers any clinical advantage in terms of its potential to induce tolerance, withdrawal symptoms, or dependence. For recommendations of the UK CSM concerning its use as a hypnotic, see Incidence of Adverse Effects, below.

References.
1. Noble S, *et al.* Zopiclone: an update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 1998; 55: 277–302.
2. Hajak G. A comparative assessment of the risks and benefits of zopiclone: a review of 15 years' clinical experience. *Drug Safety* 1999; 21: 457–69.
3. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; 26: 261–82.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

There have been reports[1,2] of zopiclone dependence and associated withdrawal symptoms on dosage reduction or cessation of use. However, a 67-year-old man who increased his dosage of zopiclone up to 337.5 mg daily to treat insomnia without apparent adverse effects, had his zopiclone withdrawn without severe complications over 4 weeks using drug and cognitive therapy.[3] A WHO expert committee[4] considered in 2006 that the likelihood of zopiclone abuse was low and not great enough to warrant international control.

1. Jones IR, Sullivan G. Physical dependence on zopiclone: case reports. *BMJ* 1998; 316: 117.
2. Sikdar S. Physical dependence on zopiclone. *BMJ* 1998; 317: 146.
3. Kuntze MF, *et al.* Excessive use of zopiclone: a case report. *Swiss Med Wkly* 2002; 132: 523.
4. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3. A bitter or metallic taste in the mouth has been the most frequently reported adverse effect with zopiclone.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to adults or children who present within one hour of ingesting more than 1 mg/kg of zopiclone. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zopiclone toxicity. (See also Overdosage, below).

Incidence of adverse effects. In a French postmarketing survey[1] of 20 513 patients treated with zopiclone, the most commonly reported adverse events were bitter taste (3.6%), dry mouth (1.6%), difficulty arising in the morning (1.3%), sleepiness (0.5%), nausea (0.5%), and nightmares (0.5%). The UK CSM[2] had received 122 reports of adverse reactions to zopiclone over a period of about one year, since the product's introduction in November 1989. A fifth of these were neuropsychiatric reactions, a proportion similar to that found with other hypnotics. Many of these reactions were potentially serious and involved hallucinations (3 auditory and 2 visual), amnesia (4 cases), and behavioural disturbances (10, including 3 cases of aggression). Most reactions started immediately or shortly after the first dose and improved rapidly on stopping the drug. Three patients had difficulty in stopping treatment, 2 because of withdrawal symptoms and one due to repeated rebound insomnia. The CSM considered that, although differing structurally from the benzodiazepines, zopiclone has the same potential for adverse psychiatric reactions, including dependence. As with the benzodiazepines it should be reserved for patients with severe sleep disturbance and its duration of use limited to 28 days; care should also be taken in the elderly, those who have a history of previous psychiatric illness, or who are prone to drug abuse.

1. Allain H, *et al.* Postmarketing surveillance of zopiclone in insomnia: analysis of 20,513 cases. *Sleep* 1991; 14: 408–13.
2. CSM. Zopiclone (Zimovane) and neuro-psychiatric reactions. *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244486&RevisionSelectionMethod=LatestReleased (accessed 20/07/09)

Abuse. For a report of zopiclone abuse see under Dependence and Withdrawal, above.

Administration. Results in 9 healthy subjects given zopiclone indicated a significant delay in onset of action when the drug was taken in the supine, as opposed to the standing, position; this was associated with a prolongation of more than 20 minutes in the lag time before absorption began.[1] In order to obtain a rapid and complete hypnotic effect from zopiclone the tablet should be swallowed in the standing position.

1. Channer KS, *et al.* The effect of posture at the time of administration on the central depressant effects of the new hypnotic zopiclone. *Br J Clin Pharmacol* 1984; 18: 879–86.

Driving. For reference to the increased risk of road-traffic accidents for drivers taking benzodiazepines, see p. 1067.1.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zopiclone, see under Zolpidem, p. 1117.2.

Hepatic impairment. Zopiclone was given in a dose of 7.5 mg to 7 cirrhotic patients and 8 healthy subjects; a further 2 cirrhotic patients received 3.75 mg.[1] Mean peak plasma concentrations were similar in healthy subjects and those with hepatic impairment following equivalent doses but time to peak plasma concentration was 4 hours in the latter as compared with 2 hours in the healthy subjects. Elimination was greatly prolonged in cirrhotic patients, in whom the mean plasma half-life was 8.53 hours compared with 3.5 hours. The CNS-depressant effects of zopiclone were delayed in the cirrhotic patients in a way consistent with the pharmacokinetic changes. There was also some evidence of an increased response in these patients.

1. Parker G, Roberts CJC. Plasma concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; 16: 259–65.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zopiclone, see under Zolpidem, p. 1117.2.

Overdosage. Fatalities have been reported after zopiclone overdose.[1,2] Methaemoglobinaemia and renal failure have been reported in a patient who took 2.25 g of zopiclone in a suicide attempt.[3]

Flumazenil may rarely be used to reverse the effects of severe zopiclone toxicity, see Non-benzodiazepine Antagonism under Flumazenil, p. 1552.2.

1. Boniface PJ, Russell SGG. Two cases of fatal zopiclone overdose. *J Anal Toxicol* 1996; 20: 131–3.
2. Meatherall RC. Zopiclone fatality in a hospitalized patient. *J Forensic Sci* 1997; 42: 340–3.
3. Kung SW, *et al.* Zopiclone-associated methemoglobinemia and renal impairment. *Clin Toxicol* 2008; 46: 1099–1100.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zopiclone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1. Use with rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4, such as carbamazepine or phenytoin, is likely to reduce the effects of zopiclone.

Antibacterials. In a study in healthy subjects *erythromycin* increased the rate of absorption of zopiclone and prolonged its elimination.[1] In another study[2] in 8 healthy subjects *rifampicin* was associated with an 82% reduction in the area under the curve for zopiclone. The peak plasma concentration of zopiclone was reduced from 76.9 to 22.5 nanograms/mL and the elimination half-life from 3.8 to 2.3 hours.

1. Aranko K, *et al.* The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; 38: 363–7.
2. Villikka K, *et al.* Concentrations and effects of zopiclone are greatly reduced by rifampicin. *Br J Clin Pharmacol* 1997; 43: 471–4.

Pharmacokinetics

Zopiclone is rapidly absorbed and widely distributed after oral doses. It has an elimination half-life of 3.5 to 6.5 hours and is reported to be about 45 to 80% bound to plasma proteins. Zopiclone is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4 and, to a lesser extent, CYP2C8; the 2 major metabolites, the less active zopiclone *N*-oxide and the inactive *N*-desmethylzopiclone, are excreted mainly in the urine. About 50% of a dose is converted by decarboxylation to inactive metabolites, which are partly eliminated via the lungs as carbon dioxide. Only about 5% of a dose appears unchanged in the urine and about 16% appears in the faeces. Excretion of zopiclone in the saliva may explain reports of a bitter taste. It is also distributed into breast milk.

Reviews.

1. Fernandez C, *et al.* Clinical pharmacokinetics of zopiclone. *Clin Pharmacokinet* 1995; 29: 431–41.
2. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; 43: 227–38.

Distribution into breast milk. Zopiclone was distributed into breast milk in 12 women in concentrations about half those in plasma.[1] The calculated dose that would be received by a neonate was 1.5 micrograms/kg, corresponding to 1.2% of the maternal dose.

1. Matheson I, *et al.* The excretion of zopiclone into breast milk. *Br J Clin Pharmacol* 1990; 30: 267–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Foltran; Imovane; Insomnium; *Austral.*: Imovane; Imrest; *Austria*: Somnal; *Belg.*: Imovane; *Braz.*: Imovane; *Canad.*: Imovane; Rhovane; *Chile*: Alpaz; Imovane; Losopil; Zetix; Zometic; Zonix; *China*: Imovane (忆梦返); Jin Meng (金盟); Qing Er Qi (青尔齐); San Chen (三辰); Cz.: Zopitin; *Denm.*: Imodone; Imovane; Imozop; *Fin.*: Imovane; Zopinox; Zopitin; *Fr.*: Imovane; *Ger.*: Optidorm; Somnosan; Ximovan; Zop†; Zopi-Puren†; *Gr.*: Imovane; *Hong Kong*: Dopareel; Eurovan; Imolone†; Imovane; Zoliel; Zomni; *Hung.*: Imovane; Somnol; Zopigen; *India*: Lyzop; Zopicon; *Irl.*: Zileze; Zimodone; Zimovane; Zopitan; Zorclone; *Israel*: Imovane; Nocturno; *Ital.*: Imovane; *Malaysia*: Imovane; Insopin; Zolon; *Mex.*: Imovane; *Neth.*: Imovane; *Norw.*: Imovane; *NZ*:

Imovane; *Pol.*: Dobroson; Imovane; Senzop; Zopiratio; *Rus.*: Imovane (Имован); Milovan (Милован); Piclodorm (Пиклодорм); Relaxon (Релаксон); Slipvell (Слипвэлл); Somnol (Сомнол); Torson (Торсон); Zolinox (Золинокс); *S.Afr.*: Adco-Zopimed; Alchera; Imovane; Z-Dorm; Zopigen; Zopivane; *Singapore*: Imovane; *Spain*: Datolan; Limovan; Siaten; Zopicalma; *Swed.*: Imovane; *Switz.*: Imovane; *Turk.*: Imovane; *UK*: Zimovane; *Ukr.*: Imovane (Имован); Normason (Нормасон); Piklon (Пиклон); Sonnat (Соннат).

Pharmacopoeial Preparations
BP 2014: Zopiclone Tablets.

Zotepine *(BAN, rINN)*

Zotepina; Zotépine; Zotepinum; Зотепин.
2-[(8-Chlorodibenzo[*b,f*]-thiepin-10-yl)oxy]-*N,N*-dimethylethylamine.
$C_{18}H_{18}ClNOS$=331.9
CAS — 26615-21-4.
ATC — N05AX11.
ATC Vet — QN05AX11.
UNII — U29O83JAZW.

Profile

Zotepine is an atypical antipsychotic that, in addition to its antagonist action at central dopamine (D_1 and D_2) receptors, binds to serotonin ($5\text{-}HT_2$), adrenergic (α_1), and histamine (H_1) receptors and also inhibits noradrenaline reuptake. It has been given in the treatment of schizophrenia (below) in an initial oral dose of 25 mg three times daily, increased according to response, at intervals of 4 days, to a maximum of 100 mg three times daily. There is an appreciable increase in the incidence of seizures at doses above 300 mg daily. For elderly patients, a starting dose of 25 mg has been given twice daily, increased gradually up to a maximum of 75 mg twice daily. Doses should also be reduced in patients with hepatic or renal impairment, see below.

Zotepine has uricosuric properties and should not be given to patients with acute gout or a history of nephrolithiasis; it should be used with caution in patients with a history of gout or hyperuricaemia.

Administration in hepatic or renal impairment. For patients with renal or hepatic impairment, an initial oral dose of zotepine 25 mg has been given twice daily, increased gradually up to a maximum of 75 mg twice daily.

Schizophrenia. A systematic review[1] of short-term studies of zotepine for schizophrenia (p. 1031.3) concluded tentatively that it was as effective as classical antipsychotics and might be of benefit in patients with negative symptoms; in addition, it seemed less likely to provoke extrapyramidal disorders. A later systematic review[2] that compared zotepine with other atypical antipsychotics found insufficient evidence for a meaningful comparison to be drawn.

1. DeSilva P, *et al.* Zotepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/04/08).
2. Subramanian S, *et al.* Zotepine versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 03/06/13).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Nipolept†; *Cz.*: Zoleptil; *Ger.*: Nipolept†; *Indon.*: Lodopin; *Jpn*: Lodopin; Losizopilon; Majorpin; Setous; *Port.*: Zoleptil; *Turk.*: Zoleptil; *UK*: Zoleptil†.

Zuclopenthixol *(BAN, rINN)*

AY-62021 (clopenthixol or clopenthixol hydrochloride); *cis*-Clopenthixol; *a*-Clopenthixol; *Z*-Clopenthixol; N-746 (clopenthixol or clopenthixol hydrochloride); NSC-64087 (clopenthixol); Tsuklopentiksoli; Zuclopenthixolum; Zuclopentixol; Zuklopentixol; Зуклопентиксол.
(*Z*)-2-[4-[3-(2-Chloro-10*H*-dibenzo[*b,e*]thiin-10-ylidene)propyl]piperazin-1-yl]ethanol.
$C_{22}H_{25}ClN_2OS$=401.0
CAS — 53772-83-1 (zuclopenthixol); 982-24-1 (clopenthixol).
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 471SU063SG.

NOTE. Clopenthixol (*BAN, INN, USAN*) is a mixture of the *Z* and *E* isomers.

Zuclopenthixol Acetate *(BANM, rINNM)*

Acetato de zuclopentixol; Zuclopenthixol, Acétate de; Zuclopenthixoli Acetas; Zuclopentixol, acetato de; Zuklopentiksol Asetat; Зуклопентиксола Ацетат.
$C_{24}H_{27}ClN_2O_2S$=443.0
CAS — 85721-05-7.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 349S2ZHF05.

Pharmacopoeias. In *Br.*

BP 2014: (Zuclopenthixol Acetate). A yellowish, viscous oil. Very slightly soluble in water; very soluble in alcohol, in dichloromethane, and in ether. Store at a temperature not exceeding -20 degrees. Protect from light.

Zuclopenthixol Decanoate *(BANM, rINNM)*

Decanoato de zuclopentixol; Tsuklopentiksolidekanoaatti; Zuclopenthixol, Décanoate de; Zuclopenthixoldecanoat; Zuclopenthixoli decanoas; Zuclopentixol, decanoato de; Zuklopenthixol-dekanoät; Zuklopentiksol Dekanoat; Zuklopentiksolio dekanoatas; Zuklopentixoldekanoat; Zuklopentyksolu dekanonian; Зуклопентиксола Деканоат.
$C_{32}H_{43}ClN_2O_2S$=555.2
CAS — 64053-00-5.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — TSS9KIZSOG.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Zuclopenthixol Decanoate). A yellow viscous oily liquid. Very slightly soluble in water; very soluble in alcohol and in dichloromethane. Store under an inert gas in airtight containers at a temperature not exceeding -20 degrees. Protect from light.

Zuclopenthixol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de zuclopentixol; Zuclopenthixol, Chlorhydrate de; Zuclopenthixol Dihydrochloride; Zuclopenthixoli Hydrochloridum; Zuclopentixol, hidrocloruro de; Zuklopentiksol Dihidroklorür; Зуклопентиксола Гидрохлорид.
$C_{22}H_{25}ClN_2OS,2HCl$=473.9
CAS — 58045-23-1.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 7042692VYN.

Pharmacopoeias. In *Br.*

BP 2014: (Zuclopenthixol Hydrochloride). An off-white granular powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; 32: 25–9.

Uses and Administration

Zuclopenthixol is a thioxanthene of high potency with general properties similar to the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain.

Zuclopenthixol is used for the treatment of schizophrenia (below), mania (see Bipolar Disorder, p. 397.2), and other psychoses. It may be particularly suitable for agitated or aggressive patients who may become over-excited with flupentixol. Zuclopenthixol hydrochloride is usually given orally with doses expressed in terms of the base; zuclopenthixol hydrochloride 11.8 mg is equivalent to about 10 mg of zuclopenthixol. Zuclopenthixol hydrochloride has also been given intramuscularly. Zuclopenthixol acetate and zuclopenthixol decanoate are given by deep intramuscular injection; doses are expressed in terms of the ester. The acetate ester has a rapid onset of action and a duration of action of 2 to 3 days; it is used as a 5% oily solution for the initial treatment of acute psychoses and for exacerbations of chronic psychoses. The longer-acting decanoate ester is used as a 20% oily solution for the maintenance treatment of chronic psychoses; a 50% solution is available for those requiring high doses.

- The usual initial *oral* dose of the hydrochloride for the treatment of psychoses is the equivalent of 20 to 30 mg of the base daily in divided doses; in severe or resistant cases up to 150 mg daily has been given. The recommended maximum single dose is 40 mg. The usual maintenance dose is 20 to 50 mg daily.
- The usual dose of zuclopenthixol acetate is 50 to 150 mg by deep *intramuscular* injection repeated, if necessary, after 2 or 3 days. Some patients may need an additional injection between 1 and 2 days after the first dose.

Zuclopenthixol acetate is not intended for maintenance treatment; no more than 4 injections should be given in a maximum course of 2 weeks and the total dose should not exceed 400 mg. When maintenance treatment is required, *oral* zuclopenthixol hydrochloride may be introduced 2 to 3 days after the last injection of zuclopenthixol acetate, or *intramuscular* injections of the decanoate (see below) begun with the last injection of the acetate.

- The long-acting decanoate should be given by deep *intramuscular* injection; treatment is usually started with a test dose of 100 mg. This may be followed after at least 1 week by a dose of 200 to 500 mg or more, every 1 to 4 weeks, adjusted according to response. Injection volumes greater than 2 mL should be divided between 2 separate injection sites. The maximum recommended dose of zuclopenthixol decanoate is 600 mg weekly.

Elderly or debilitated patients should be given reduced doses of zuclopenthixol. Licensed product information states that the dose of the hydrochloride or the decanoate may need to be reduced to one-quarter or one-half of the usual initial dose; in addition, the maximum single dose of the acetate should be limited to 100 mg.

Dosage adjustment is also advised in patients with hepatic or renal impairment (see below).

Administration in hepatic or renal impairment. Licensed product information recommends that for both zuclopenthixol acetate and hydrochloride, half the usual recommended intramuscular and oral dose, respectively, should be used for patients with hepatic impairment; a dosage reduction is considered to be unnecessary in patients with renal impairment but where there is renal failure half the usual dosage is recommended.

Schizophrenia. A systematic review[1] comparing zuclopenthixol decanoate with other depot antipsychotics considered that although it may induce more adverse effects, limited data suggested it might offer advantages such as lower relapse rates and increased acceptability in the treatment of schizophrenia (p. 1031.3) and similar serious mental illnesses. Similar reviews of the use of the acetate[2] or hydrochloride[3] found, however, that evidence of additional benefit over other antipsychotics was lacking.

1. Coutinho E, *et al.* Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 14/04/05).
2. Gibson RC, *et al.* Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).
3. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 12/05/06).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Zuclopenthixol is less likely to cause sedation but extrapyramidal effects are more frequent.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zuclopenthixol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Zuclopenthixol is absorbed after oral doses and peak plasma concentrations occur 3 to 6 hours later. The biological half-life after oral doses is reported to be about 1 day. Paths of metabolism of zuclopenthixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. It is mainly excreted in the faeces as unchanged drug and its *N*-dealkylated metabolite. Zuclopenthixol is about 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Small amounts of drug or metabolites cross the placenta and are distributed into breast milk.

On intramuscular injection the acetate and decanoate esters of zuclopenthixol are hydrolysed to release zuclopenthixol. Zuclopenthixol acetate has a relatively quick onset of action after injection and a duration of action of 2 to 3 days. It is therefore useful for the control of acute psychotic symptoms while avoiding repeated injections. The decanoate has a much longer duration of action and is a suitable depot preparation for maintenance treatment.

Metabolism. Determination of metaboliser phenotype with regard to cytochrome P450 isoenzyme CYP2D6 appeared to be of limited value in patients receiving zuclopenthixol as interindividual variation appeared to be

the main factor affecting dose to serum concentration ratios.[1]

1. Linnet K, Wiborg O. Influence of Cyp2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopenthixol. *Ther Drug Monit* 1996; **18**: 629–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clopixol; ***Austral.***: Clopixol; ***Austria***: Cisordinol; ***Belg.***: Clopixol; ***Braz.***: Clopixol; ***Canad.***: Clopixol; ***Chile***: Cisordinol; ***China***: Clopixol (高抗素); ***Cz.***: Cisordinol; ***Denm.***: Cisordinol; Clopixol; ***Fin.***: Cisordinol; ***Fr.***: Clopixol; ***Ger.***: Clatyl-Z; ***Gr.***: Clopixol; ***Hong Kong***: Clopixol; ***Hung.***: Cisordinol; ***India***: Clopixol; ***Irl.***: Clopixol; ***Israel***: Clopixol; ***Ital.***: Clopixol; ***Malaysia***: Clopixol; ***Mex.***: Clopixol; ***Neth.***: Cisordinol; Clopixol; ***Norw.***: Cisordinol; ***NZ***: Clopixol; ***Philipp.***: Clopixol†; ***Pol.***: Clopixol; ***Port.***: Cisordinol; ***Rus.***: Clopixol (Клопиксол); ***S.Afr.***: Clopixol; Colpixol†; ***Singapore***: Clopixol; ***Spain***: Clopixol; ***Swed.***: Cisordinol; ***Switz.***: Clopixol; ***Thai.***: Clopixol; ***Turk.***: Clopixol; ***UK***: Clopixol; ***Ukr.***: Clopixol (Клопиксол).

Pharmacopoeial Preparations

BP 2014: Zuclopenthixol Acetate Injection; Zuclopenthixol Decanoate Injection; Zuclopenthixol Tablets.

Blood Products Plasma Expanders and Haemostatics

This chapter describes the management of blood disorders including some anaemias, haemorrhagic disorders, and neutropenia. It covers blood, blood products and substitutes, and colloid plasma expanders; crystalloid plasma expanders are generally solutions of sodium chloride (p. 1797.3) or glucose (p. 2068.3) or both. Also included in the chapter are haemostatic drugs and erythropoietin and other colony-stimulating factors. The management of haematological malignancies is covered in the Antineoplastics chapter, p. 691.1.

Haematopoiesis

In the embryo and fetus, the formation and development of blood cells occurs at various sites including the liver, spleen, thymus, lymph nodes, and bone marrow; from birth throughout the rest of life it occurs mainly in the bone marrow with a small amount occurring in the lymph nodes. The bone marrow contains pluripotent stem cells that differentiate into different types of progenitor cells (committed stem cells); these then mature into various types of blood cells under the influence of growth factors and hormones. The main cellular components of blood are red blood cells (erythrocytes), white blood cells (leucocytes), and platelets.

Erythrocyte production is stimulated by erythropoietin, a hormone released by the kidney in response to anaemia or hypoxia.

The leucocytes are classified according to their morphological appearance into granulocytes, lymphocytes, and monocytes. The granulocytes are further classified as neutrophils, eosinophils, and basophils, according to the characteristics of their cytoplasmic granules. The term polymorphonuclear leucocytes can be applied to granulocytes in general but applies in particular to neutrophils. Most lymphocytes are matured in the lymph nodes, thymus, and spleen, from bone marrow lymphocyte precursors. Lymphocytes enter the bloodstream via the lymphatics, but only a small proportion are present in the blood. Monocytes are released into the blood but then enter the tissues to become fixed tissue macrophages. The maturation of leucocytes is stimulated by granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF).

Platelet maturation is stimulated by thrombopoietin.

Other growth factors involved at various stages of blood cell development include stem cell factor and interleukins-1, -3, -4, -5, -6, and -11.

The average blood cell counts in adults are:

- erythrocytes (men): 5.0×10^{12} cells/litre
- erythrocytes (women): 4.3×10^{12} cells/litre
- leucocytes: 7.0×10^{9} cells/litre (7000 cells/mm^3) but the value can vary markedly, even in the same individual at different times, from 4 to 11×10^{9} cells/litre. This total is made up of:
  neutrophils (40 to 80%)
  lymphocytes (20 to 40%)
  monocytes (2 to 10%)
  eosinophils (1 to 6%)
  basophils (< 1 to 2%)
- platelets: 150 to 450×10^{9} cells/litre (150 000 to 450 000 cells/mm^3)

Anaemias

Anaemia is usually understood to mean a lowering of haemoglobin concentration, red cell count, or packed cell volume to below 'normal' values, but the criteria for normality are difficult to establish. WHO's suggested definition of anaemia in populations living at around sea level is a haemoglobin concentration below:

- 13 g per 100 mL in men
- 12 g per 100 mL in women
- 11 g per 100 mL in pregnant women
- 12 g per 100 mL in children aged 12 to 14 years
- 11.5 g per 100 mL in children aged 5 to 11 years
- 11 g per 100 mL in children aged 6 to 59 months

However, because of individual variation, some apparently normal individuals have blood haemoglobin concentrations below these values, while others may be above these values and still be effectively anaemic.

Reduction in overall haemoglobin concentrations may be due to fewer red cells, with the cells retaining normal amounts of haemoglobin (normochromic anaemia), or the amount of haemoglobin in the cells may be reduced (hypochromic anaemia). Red cells themselves may be reduced in size (microcytic), enlarged (macrocytic), or normal in size (normocytic).

The immediate cause of anaemia may be decreased red cell production (due to defective proliferation and/or maturation of red cells from their precursors in bone marrow), increased red cell destruction (i.e. haemolysis), or loss of red cells from the circulation due to haemorrhage, either occult or overt. These conditions may occur due to underlying disease, nutritional deficiency, congenital disorders, or toxicity due to drugs or other substances and the cause must always be sought before an appropriate treatment can be determined.

The symptoms of anaemia are as variable as its causes but may include fatigue, pallor, dyspnoea, palpitations, headache, faintness or lightheadedness, tinnitus, anorexia and gastrointestinal disturbances, and loss of libido; tachycardia, heart failure, and retinal haemorrhage may occur in severe anaemia.

The treatment of anaemia depends upon its type and cause. Some of the principal types are classified in Table 1, below, and their management is discussed in more detail under the relevant headings. Sickle-cell disease and β-thalassaemia are discussed under Haemoglobinopathies, p. 1123.2.

Table 1. Types of anaemias.

Classification	Anaemia	Mean cell volume	Haemoglobin	Associated with
Microcytic	Iron-deficiency anaemia	Decreased (or normal in early stages)	Hypochromic	Blood loss, malabsorption, inadequate iron intake
	Hereditary sideroblastic anaemia	Decreased	Hypochromic	
	Thalassaemias	Decreased	Hypochromic	
Macrocytic	Megaloblastic anaemia	Increased	Normochromic	Vitamin B_{12} deficiency, folate deficiency (including drug induced)
	Acquired sideroblastic anaemia	Increased	Hypochromic	Alcoholism, drug or other toxicity
Normocytic	Normocytic-normochromic anaemia	Normal	Normochromic	Anaemia of chronic disorders, bone-marrow disorders (including aplastic anaemia), malignancy, renal failure, endocrine disorders, prematurity
Haemolytic	Haemolytic anaemia	Increased		Immune disorders, drug toxicity, hereditary disorders
	Sickle-cell anaemia			

The symbol † denotes a preparation no longer actively marketed

Reviews.
1. Spivak JL. The blood in systemic disorders. *Lancet* 2000; 355: 1707–12.
2. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. *Mayo Clin Proc* 2003; 78: 1274–80.
3. Tefferi A. Practical algorithms in anemia diagnosis. *Mayo Clin Proc* 2004; 79: 955–6.

Aplastic anaemia

Aplastic anaemia is characterised by pancytopenia (a deficiency of all cellular elements of the blood) and hypoplasia of the bone marrow, with less than 25% of the marrow occupied by haematopoietic cells but without evident fibrosis or malignant infiltration. It is relatively rare, although it may be somewhat more common in the Far East, and is mainly seen in younger adults. Some forms, such as Fanconi's anaemia, are inherited but most are induced, for example by the effects of cytotoxic drugs or radiation, idiosyncratic reactions to other drugs, seronegative fulminant hepatitis, or auto-immune reactions. Since all cell lines are affected patients develop thrombocytopenia and neutropenia as well as anaemia, and symptoms include bleeding syndromes and infections as well as typical symptoms of anaemia. Paroxysmal nocturnal haemoglobinuria (see Haemolytic Anaemia, p. 1122.2), in which genetic mutation causes the production of abnormal blood cells and results in haemolysis, can be associated with aplastic anaemia.

Although spontaneous recovery has occurred, untreated aplastic anaemia is usually fatal. Management may be divided into supportive care and attempts to restore bone-marrow function with bone marrow transplantation or immunosuppression, and has been the subject of guidelines and reviews.[1-4]

Supportive care involves the prevention and treatment of infection (see Infections in Immunocompromised Patients, p. 186.3), the control of haemorrhage with platelet concentrates, and where necessary, infusions of red

blood cells (with platelets to prevent haemorrhage) for anaemia. The risk of developing alloimmunisation, which can result in platelet refractoriness and increase the risk of graft rejection after allogeneic bone marrow transplantation, may be reduced by the use of leucocyte-depleted red cells and platelets. Some guidelines[4] also recommend the use of irradiated blood products in patients receiving antilymphocyte immunoglobulin, although evidence to support this is lacking and practice varies worldwide.

In patients aged under 40 years with *severe disease* and with a suitable HLA-identical sibling donor, **bone marrow transplantation** offers the prospect of long-term cure, and is considered the treatment of choice.[1,2,4,5] Ideally this should be performed early before the patient has received too many transfusions, which increase the risk of rejection, and before infection develops. Bone marrow stem cells are recommended because chronic graft-versus-host disease and overall survival may be worse when peripheral blood stem cells are used.[2,4] Umbilical cord blood is an alternative source of stem cells and may be associated with less acute and chronic graft-versus-host disease than bone marrow transplantation.[4] However, the use of cord blood is limited by the low number of cells that can be obtained.

In patients unsuitable for bone marrow transplantation, or where a suitable sibling donor is not available, treatment with **immunosuppressants** may be tried. About 50% of patients are reported to respond to a course of antilymphocyte immunoglobulin, and the addition of ciclosporin further improves response rates to between 60 and 80% and 5-year survival to between 75 and 90%.[1,4] However, one long-term study[6] providing follow-up data for 11 years has found no significant difference in survival between regimens of antilymphocyte immunoglobulin with or without ciclosporin.[6] Response to treatment is usually delayed, and starts after about 3 to 4 months.[4] Ciclosporin has been used alone but is less effective than antilymphocyte immunoglobulin.[1,2]

Despite these good rates of response with the addition of ciclosporin, relapse is not uncommon.[7] A second course of antilymphocyte immunoglobulin is recommended if there is no response, or there is relapse, after 3 months.[4] Ciclosporin is continued after a response has occurred and until the blood count has been stable for at least 12 months; it may then be slowly withdrawn, usually over many months and depending on blood counts.[4] Some patients may require continued therapy.[2,3]

In patients with severe aplastic anaemia who have failed at least 1 course of antilymphocyte immunoglobulin and ciclosporin, and who are less than 50 years old, a matched unrelated bone marrow transplantation using a fludarabine-based regimen without irradiation may be considered.[4]

Good response rates have been reported from combined regimens including a granulocyte colony-stimulating factor.[8] However, there are concerns about long-term use and the role of these factors is still under investigation.[2,4,9] There has been interest in the use of other haematopoietic growth factors including granulocyte-macrophage colony-stimulating factor, ancestim (stem cell factor), epoetin, interleukin-1, interleukin-3, and interleukin-6, either alone or with immunosuppression, but results have generally been poor or studies stopped because of toxicity, and so the use of these factors is not recommended.[4,9] However, short courses of granulocyte colony-stimulating factor may be considered for supportive therapy in neutropenic patients with severe systemic infections that are not responding to antibacterial or antifungal therapy.[4] Neutrophil responses are usually seen in patients with non-severe aplastic anaemia who have residual marrow granulocytopenic activity.

Oxymetholone was used extensively before the availability of antilymphocyte immunoglobulin and ciclosporin. It can increase the response to antilymphocyte immunoglobulin alone, but it can be hepatotoxic and causes virilisation, and is generally used for patients who have failed several courses of antilymphocyte immunoglobulin with ciclosporin, or where this regimen cannot be used.[4] Cyclophosphamide is commonly used in preparation for bone marrow transplantation and complete remission has also been reported with high-dose cyclophosphamide alone.[10,11] However, a randomised study[12] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those receiving cyclophosphamide. Further follow-up[13] also found that relapse rates were no different. Nonetheless, cyclophosphamide continues to be of investigational interest.[3]

Responses to immunosuppressants are often partial, but this may be sufficient to free the patient from dependency on transfusions and intensive antibacterial cover, and is considered well worth achieving.[1] Nevertheless, the procedure is not curative; patients appear to retain some underlying defect in marrow function, and in the long term about 15% of them develop leukaemias or myelodysplasias.[1]

Children with severe aplastic anaemia are treated similarly to adults.[14,15] Although some reports have suggested that the response to immunosuppressant therapy may be lower in children under 5 years of age, others have shown the opposite.[14] The choice of treatment in children may also need to take into account the potential long-term adverse effects of treatment, particularly with immunosuppressants or irradiation, on endocrine function, growth, fertility, and the development of secondary malignancies.

Older patients tend to be treated with immunosuppressant therapy rather than bone marrow transplantation.[4] A retrospective cohort study[16] that compared patients older than 50 years with younger patients found that more older patients had received ciclosporin alone, that the response to immunosuppression was independent of age at the time of treatment, and that although survival decreased with age deaths were similar to those in a general population and were not related to the type of treatment or the number of courses of treatment.

The outcome of **pregnancy** in women who had previously been treated for aplastic anaemia with an immunosuppressant regimen has been described.[17] Of 36 pregnancies, 22 were uncomplicated and 7 were complicated by relapse of aplastic anaemia; complications appeared to be more likely in women with low platelet counts and paroxysmal nocturnal haemoglobinuria. Rarely, aplastic anaemia can develop during pregnancy, and although the disease may remit spontaneously after termination or delivery, this does not occur in all cases.[18,19] Supportive care is the mainstay for management of aplastic anaemia during pregnancy, although the use of ciclosporin may be considered if transfusions are required.[4]

Patients with *non-severe aplastic anaemia* may require supportive therapy only. However, those who are transfusion-dependent,[4,20] or who have significant neutropenia with an associated risk of infection,[4] may be candidates for immunosuppressive therapy. For children, bone marrow transplantation from an HLA-identical sibling may be considered in those with non-severe disease who are transfusion-dependent, particularly if the blood count is falling.[4]

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2. Marsh JCW. Management of acquired aplastic anaemia. *Blood Rev* 2005; 19: 143–51.
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7. Rosenfeld S, *et al.* Antithymocyte globulin and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome. *JAMA* 2003; 289: 1130–5.
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Haemolytic anaemia

The normal life span of an erythrocyte is about 120 days; a haemolytic state is defined as a reduction in this mean life span due to premature destruction of red cells, either intravascularly, or more commonly after sequestration by the spleen or liver. Healthy bone marrow can compensate for even quite severe haemolysis by increased erythropoiesis; however, if the red cell survival-time is less than 15 days, or if the bone marrow is abnormal, or there is a deficiency of folate, iron, or other necessary nutrients, then compensation will be inadequate and haemolytic anaemia will result. In addition to typical symptoms of anaemia (p. 1121.2) patients frequently have jaundice and splenomegaly, while the increased erythropoiesis results in reticulocytosis (elevated counts of immature red cells).

Haemolytic anaemias may be either congenital or acquired. The **congenital** disorders include:

- those due to membrane defects in the erythrocyte, such as spherocytosis or elliptocytosis
- those due to enzyme defects (including the various forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency)
- those due to haemoglobin defects (haemoglobinopathies), including sickle-cell disease (p. 1123.2) and β-thalassaemia (p. 1124.1)

The **acquired** haemolytic anaemias arise from many causes but may be divided into immune and non-immune types. The immune types include:

- some drug-induced haemolytic anaemias (including those produced by penicillins, rifampicin, and methyldopa)
- auto-immune haemolytic anaemia (further classified into warm or cold depending on the temperature at which the red cell antibodies are most active)
- paroxysmal nocturnal haemoglobinuria, resulting from complement-mediated red cell lysis
- haemolytic disease of the newborn (see p. 2377.2)

The non-immune types include:

- haemolysis due to infections such as malaria
- chemically-induced haemolysis (due to a direct effect on the red cell rather than an immunologically-mediated one, and including the effects of toxins such as copper and arsenic as well as some snake venoms, and drugs such as amphotericin B, dapsone, and sulfasalazine)
- the effects of mechanical trauma

Treatment of haemolytic anaemia depends on the underlying cause, although general supportive measures (bed rest, transfusion if haemodynamic abnormalities make it necessary, and supplementation with folate) will be similar in all poorly-compensated patients. Well compensated haemolysis may require no treatment at all, although clearly elucidation and, where possible, removal of the cause is desirable.

Hereditary haemolytic disorders such as spherocytosis[1] mostly respond well to splenectomy, although milder forms may not require treatment. In patients with G6PD deficiency, treatment consists essentially of avoidance of drugs or foodstuffs likely to provoke haemolysis.

Acquired haemolytic anaemia is best treated by identification and where possible elimination of any underlying cause. Most drug-induced haemolytic anaemias respond rapidly to withdrawal of the offending substance.

Auto-immune haemolytic anaemias require treatment aimed at maintaining the patient and controlling haemolysis. Although treatment may need to be prolonged, in many patients with idiopathic disease antibodies eventually disappear or decrease to insignificant titres after months or years. The auto-immune haemolytic anaemias may be secondary to other disorders including leukaemias, lymphomas, and SLE; correction of the underlying disease often results in marked improvement of accompanying haemolysis.

In patients with warm auto-immune haemolytic anaemia treatment starts with corticosteroids.[2] A typical initial dose is oral prednisone or prednisolone 1 to 1.5 mg/kg daily. The onset of response is usually rapid and most patients benefit within 10 to 14 days. The initial effective dose of corticosteroid should be continued until a satisfactory response has been obtained, and once there is haematologic stabilisation the dose may be gradually reduced. Many patients will require low-dose maintenance therapy. If symptoms do not respond to tolerable doses of corticosteroids splenectomy should be considered. Immunosuppressants such as azathioprine or cyclophosphamide may be considered in patients refractory to other therapy; responses are reportedly variable, but they sometimes permit reduction of corticosteroid maintenance doses. There are some reports of benefit from the use of danazol and some cases have responded to rituximab. High-dose intravenous normal immunoglobulin may be used in some patients if the adverse effects of long-term corticosteroid or immunosuppressant therapy are severe. Plasma exchange may be useful for acute management of severe haemolysis while other therapies are taking effect.[2] Transfusion is problematic in these patients because of the difficulty in establishing compatibility between patient and donor.[3] Nonetheless, transfusion may be life-saving in acute disease, and the least incompatible blood should be used.

In patients with cold auto-immune haemolytic anaemias such as cold haemagglutinin disease it is additionally important to keep the patient warm.[2] Corticosteroids and splenectomy are generally of no benefit in these patients (although there may be a responsive subgroup), but treatment with oral chlorambucil 2 to 4 mg daily may produce a response. Blood transfusion should be avoided if

possible, and if given it should be preferably via a warming coil and infused slowly. Rituximab has also been tried with some success in cold auto-immune haemolytic anaemia.

In paroxysmal nocturnal haemoglobinuria, red cells are more sensitive to complement-mediated lysis because of a deficiency in protective membrane proteins on the cell surface. Haemolysis may be accompanied by neutropenia, thrombocytopenia, and venous thrombosis, and in some patients there may be some overlap with aplastic anaemia, see p. 1121.3. Curative therapy for paroxysmal nocturnal haemoglobinuria is possible with allogeneic haematopoietic stem cell transplantation. More recently, eculizumab has become available; a monoclonal antibody directed at the complement protein C5, it inhibits terminal complement activation to reduce haemolysis and transfusion requirements.[4,5]

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Iron-deficiency anaemia

For a discussion of iron deficiency anaemia and its management, see under Iron, p. 2073.2.

Megaloblastic anaemia

For a discussion of megaloblastic anaemia and its management, see under Vitamin B_{12}, p. 2109.1.

Normocytic-normochromic anaemia

Anaemias in which red cell size and cellular haemoglobin are not significantly different from normal (normocytic-normochromic anaemias) form a substantial proportion of all cases. Such anaemias are usually secondary to another disease and include:

- anaemia of chronic disorders (associated with chronic infection such as tuberculosis, malignancy, inflammatory disorders such as inflammatory bowel disease, polymyalgia rheumatica, rheumatoid arthritis, and SLE)
- anaemia of renal failure
- anaemia of prematurity
- anaemia associated with endocrine disorders such as hypothyroidism or hypopituitarism
- anaemias associated with primary bone-marrow failure (including aplastic anaemia, p. 1121.3, pure red cell aplasia, marrow fibrosis or infiltration as in myelodysplasia or leukaemia, and marrow failure associated with AIDS).

Iron-deficiency anaemia (p. 2073.2), which is usually classified as microcytic and hypochromic may in fact be neither, particularly in the early stages, and should be differentiated from anaemia of chronic disease. The latter is also accompanied by changes in iron metabolism, notably sequestration of iron in reticuloendothelial cells: plasma iron is low but in contrast to iron deficiency the total iron binding capacity is reduced and serum ferritin is often increased.

The **treatment** of most of these anaemias is essentially that of the underlying disease. Blood transfusion has been given when anaemia is severe. In patients with anaemia of renal failure, which is due at least in part to decreased erythropoietin production by the damaged kidney, regular subcutaneous or intravenous injection of recombinant human erythropoietins (epoetins) can completely reverse the anaemia; darbepoetin alfa and peginesatide acetate are used similarly. Epoetins may also have a role in anaemia of prematurity and some drug-induced anaemias, and have been investigated in patients with the anaemia of chronic disease and some other normocytic-normochromic anaemias.

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Sideroblastic anaemia

The sideroblastic anaemias are characterised by a population of hypochromic red cells in the presence of increased serum-iron concentrations, and abnormal erythroid precursors, known as ring sideroblasts, in the bone marrow. They are associated with abnormalities in porphyrin biosynthesis leading to diminished production of haem, and increased mitochondrial iron uptake. Sideroblastic anaemias may be of various types, and are classified as acquired or hereditary.

Acquired sideroblastic anaemia. Acquired sideroblastic anaemia may either be idiopathic, or secondary to either a drug or toxin (such as alcohol, isoniazid, chloramphenicol, or lead) or to a disease (including hypothyroidism, rheumatoid arthritis, haemolytic or megaloblastic anaemias, leukaemias, and lymphomas). The treatment of the secondary forms is essentially the treatment of the underlying disease or removal of the precipitating cause. The anaemia is usually mild and often macrocytic.

Patients with idiopathic disease usually have only mild anaemia, and most require no treatment. Although rarely suffering from vitamin B_6 deficiency a few patients will respond at least partially to high oral doses of pyridoxine, up to 400 mg daily, and a trial is considered worthwhile in all patients. If patients become symptomatic, transfusion may be required, but should be kept to a minimum because of the problems of iron overload. All patients with sideroblastic anaemia must have their serum-iron and -ferritin concentrations regularly monitored, and be given desferrioxamine by regular bolus injection when there is evidence of iron overload. The use of epoetins and granulocyte colony-stimulating factor is under investigation.

Hereditary sideroblastic anaemia. The hereditary forms of the disease appear to be sex-linked, and almost always manifest themselves in males. The anaemia may be more severe than in acquired sideroblastic anaemia, and is usually microcytic.

A trial of pyridoxine is considered worthwhile as some forms are responsive, but in many cases there is no benefit. Some patients develop gradually increasing iron loads, and may eventually develop haemosiderosis; to prevent this, regular venesection or the use of desferrioxamine are indicated if there is evidence of iron accumulation. Allogeneic bone marrow or haematopoietic stem cell transplantation is under investigation.

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Haemoglobinopathies

Haemoglobinopathies are clinical abnormalities due to altered structure, function, or production of haemoglobin. Human haemoglobins are tetramers, constructed of 4 globin chains each enfolding an iron-containing haem moiety: two of these globins are of the 'α-like' types (globins α or ζ) and two are 'non-α' (types β, γ, δ, or ε). The normal major adult haemoglobin, haemoglobin A, comprises two α and two β chains, while the predominant fetal haemoglobin, haemoglobin F (also present in minute amounts in normal adults), is composed of two α and two γ globins. The erythroblast inherits two genes for the production of α globin and one for β globin production from each parent, and a mutation in a single α gene will therefore affect only 25% of the haemoglobin produced, whereas a single β mutation will affect 50%: the β-haemoglobinopathies, due to defective β globin production, are therefore more likely to produce symptoms, and the most widespread forms are the β-thalassaemias (p. 1124.1) and sickle-cell disease (below).

Sickle-cell disease

Sickle-cell disease is a haemoglobinopathy (see above) in which a structural abnormality in the β globin chain results in the formation of an abnormal haemoglobin, haemoglobin S. In the deoxygenated state haemoglobin S is less soluble and polymerises into rod-like fibres, and cells containing high concentrations of haemoglobin S subsequently become deformed into a sickle shape. Normal haemoglobins can be incorporated into the polymer but some, such as fetal haemoglobin (haemoglobin F), are not; increasing concentrations of these in the red cell reduce the rate of sickling.

The heterozygous form, sickle-cell trait, is generally asymptomatic except in conditions of extreme anoxia, although characteristic abnormalities of renal function (inadequate concentration of the urine) may be present. As with thalassaemia trait (see p. 1124.1) it is more common in populations of tropical origin, and has been postulated to offer a degree of protection against malaria. In the homozygous form a varying degree of haemolytic anaemia is present, accompanied by increased erythropoiesis. In addition to shortened survival, the decreased flexibility of the deformed erythrocytes can lead to occlusion of the microvasculature, and sickle-cell crisis. The latter may manifest as excruciating pain due to infarction of the blood supply to the bones, or infarction of other organs including lung, liver, kidney, penis (leading to priapism), and brain (stroke). An acute chest syndrome occurs in many patients, and may be fatal. It is a form of acute lung injury associated with infarction, fat embolism, and infection, and may progress to acute respiratory distress syndrome. Occasionally a large proportion of red cell mass may become trapped in the spleen or liver (sequestration crisis) with death due to gross anaemia. Chronic complications include skin ulceration, renal failure, retinal detachment, and increased susceptibility to infection.

Treatment of sickle-cell disease is essentially symptomatic.[1-7] Young children should receive prophylactic penicillin and pneumococcal vaccine, to reduce the risk of infection (see Spleen Disorders, p. 207.3). Infection should be treated early, and folate supplementation given if necessary since the increased erythropoiesis resulting from chronic haemolysis may increase folate requirements.

Sickle-cell crisis requires hospitalisation, with the use of large volumes of intravenous fluids for dehydration, analgesia including opioids for pain (see p. 11.1), and treatment of any concurrent infection. Oxygen should be given if the patient is hypoxaemic. Where crisis affects a vital organ with life-threatening or potentially disabling consequences partial exchange transfusion should be carried out promptly, as no other therapy exists. Where rapid enlargement of spleen or liver indicates a sequestration crisis, transfusion is also important to avoid fatal anaemia.

Maintenance transfusion is rarely indicated, although it may be given to patients who have already had a stroke; measures to avoid iron overload such as phlebotomy or desferrioxamine chelation are necessary in patients receiving regular transfusions. Prophylactic transfusions in children at high risk have been reported[8] to reduce the incidence of first stroke but the risks and benefits of treatment must be carefully considered. A further study[9] investigated whether prophylactic transfusions could be safely stopped after 30 months in children who had not had an overt stroke and who had reverted to low stroke risk. The study was stopped early when it was found that in those who stopped transfusions there was a significant return to high risk and that some patients had subsequently suffered a stroke. Splenectomy may be recommended in the management of recurrent splenic sequestration.

Research into specific therapy for sickling has produced some promising results. Because haemoglobin F is known to protect against sickling, considerable interest has centred on attempts to stimulate fetal haemoglobin production. Most studies have used hydroxycarbamide. Initial results showed some elevation in mean fetal haemoglobin concentrations, but responses were very variable. However, a subsequent randomised controlled study in 299 patients[10] reported that therapy with hydroxycarbamide caused a 44% reduction in the median annual rate of painful crises. The beneficial effects did not become evident for several months. Observational follow-up of 233 patients in this group,[11] for up to 9 years, suggested that hydroxycarbamide also reduced mortality. Beneficial effects have also been reported in initial studies in children[12-14] and sustained benefits have been reported in longer-term cohort studies.[15,16] Results from a small study[17] in children suggested that hydroxycarbamide, with serial phlebotomy to reduce iron overload, may be an effective replacement for secondary stroke prophylaxis in patients who are unable to continue with long-term maintenance transfusions. Although one study,[16] in which some children had received hydroxycarbamide for up to 8 years, found no evidence of mutagenic changes or cases of malignancy, the potential toxicity of long-term therapy remains a concern. A short-chain fatty acid, butyric acid, which has a low order of toxicity, has been reported to stimulate fetal haemoglobin in patients with sickle-cell disease when given by infusion as arginine butyrate.[18] Promising results have also been reported in small studies[19] using oral sodium phenylbutyrate. Other drugs under investigation include clotrimazole, decitabine, inhaled nitric oxide, and the nonionic surfactant poloxamer 188. There is also some investigation into gene therapy.

As in thalassaemia (see p. 1124.1), bone marrow transplantation is potentially curative in a small minority of patients, but the indications for transplantation are much less well established.[20]

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β -Thalassaemia

β-Thalassaemia is a haemoglobinopathy (p. 1123.2) that is due to a deficiency in β globin production accompanied by normal production of α globin chains that, in the absence of sufficient partner chains, are insoluble and precipitate out in erythrocytes and erythroid precursors as large cellular inclusions. These interfere with red cell maturation resulting in ineffective haematopoiesis, retard the passage of red cells from the bone marrow, and create a tendency for those red cells that do mature to be trapped and destroyed in the spleen. The condition is therefore characterised by a hypochromic, microcytic anaemia accompanied by haemolysis. In the heterozygous form, where only one of the β globin genes is affected (known as thalassaemia trait or thalassaemia minor) the anaemia is mild and clinically insignificant. There is some evidence that patients with this form of the disease have a degree of protection from malaria, which may account for the more frequent distribution of the trait in the populations of areas such as the Mediterranean, parts of Africa, and Asia.

The more severe forms of the disease (known as thalassaemia intermedia if haemoglobin levels are high enough not to require regular transfusion, or thalassaemia major in transfusion-dependent patients) occur in homozygous patients who inherit a defective β globin gene from both parents. Severe anaemia develops in the first year of life as fetal haemoglobin production (which does not involve a β globin) is replaced by the production of adult haemoglobin. The anaemia stimulates erythropoietin production, and if not corrected massive proliferation of red cell precursors develops within, and eventually beyond, the bone marrow, resulting in recurrent bone fractures, deformity of the skull due to expansion of the marrow spaces, and compression of vital structures such as the spinal cord with consequent paresis. Other symptoms include splenomegaly and hypersplenism (resulting in neutropenia and thrombocytopenia), increased susceptibility to infection, and hypermetabolism which may lead to folate deficiency because of the increased folate requirement. If untreated, death in patients with thalassaemia major usually occurs by the 2nd or 3rd year.

Treatment. The mainstay of treatment for severe β-thalassaemia is regular blood transfusion to correct the anaemia. Transfusions should be started as early as possible in life once it is clear that anaemia is severe enough to warrant them. Various transfusion regimens have been used based on different pretransfusion haemoglobin concentrations.[1] The Thalassaemia International Federation[2] recommends regular blood transfusions, usually every 2 to 5 weeks, to maintain the pretransfusion haemoglobin concentration above 9 to 10.5 g per 100 mL. A higher target of 11 to 12 g per 100 mL may be appropriate for patients with heart disease. The post-transfusion concentration should not exceed 14 to 15 g per 100 mL. It is also recommended that patients should receive leucocyte-depleted packed red cells in order to minimise adverse reactions and platelet allo-immunisation (an immune response to donor platelets). Washed red cells may be used in patients who have repeated severe allergic transfusion reactions. The use of leucocyte-depleted red cells is also desirable in patients who are candidates for haematopoietic stem cell transplantation to reduce the risk of graft rejection and CMV reactivation.[1] An increase in transfusion requirements is a sign of hypersplenism, and splenectomy may be indicated depending on the state of iron overload. However, splenectomy should be avoided if possible below the age of 5 years because of the increased risk of overwhelming sepsis.[2] For a discussion of antibacterial prophylaxis in splenectomised patients, see Spleen Disorders, p. 207.3.

If anaemia is corrected by transfusion, growth and development proceed fairly normally in thalassaemic children. However, because the body lacks a mechanism for the excretion of excess iron, repeated transfusion invariably results in iron overload (p. 1545.2), leading eventually to haemochromatosis. The consequences of haemochromatosis include liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and particularly heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up usually leads to death (mainly through heart failure or arrhythmia) by the time patients reach their mid-20s. The accumulation of iron can be retarded by the chelator desferrioxamine and regular systemic use has been shown to improve survival in thalassaemic children,[2,3] and to protect against the cardiac complications of iron overload.[2-4] Ideally, continuous administration of iron chelation therapy optimises iron excretion. Desferrioxamine is usually given by subcutaneous infusion over 8 to 12 hours, several times a week. Alternatively, twice daily subcutaneous boluses may be considered if an infusion pump is not available or prolonged infusion is not tolerated in patients who are not at high risk of heart disease. Continuous 24-hour intravenous infusion may be considered in patients with severe iron overload or significant cardiac complications, or when rapid reversal of iron loading is desirable before pregnancy or bone marrow transplantation.[2] There is some suggestion that intensive desferrioxamine therapy can improve impaired organ function,[3] but it is considered preferable to begin chelation therapy as early as possible to try to prevent organ damage developing in the first place. In practice, desferrioxamine therapy is started after the first 10 to 20 transfusions or when the ferritin concentration rises above 1 mg/litre, usually at about 3 years of age.[2,5] If therapy is started before this age, careful monitoring of growth and bone development is recommended[2] and liver biopsy has been advocated.[3] Better iron excretion is achieved if patients are given oral ascorbic acid supplements in addition to desferrioxamine (but see under Interactions for Desferrioxamine, p. 1547.3). Patients with thalassaemia may have increased folate requirements and folate supplementation may also be necessary. Although it is not yet certain how much chelation therapy will prolong survival the fact that a nearly normal iron balance can be achieved long term seems hopeful. Deferiprone has been used as an oral alternative to desferrioxamine,[4] but there are conflicting reports regarding its efficacy and safety in the longer term.[7,8] It may have a role in patients for whom desferrioxamine therapy is unsuitable.[2] Combination therapy using desferrioxamine with deferiprone is under investigation,[5] and may be considered when monotherapy is insufficient to control levels of iron or when there is significant heart disease.[2] Deferasirox is another oral chelator that has become available more recently.[2]

In addition to the essentially symptomatic treatment of thalassaemia there is growing experience with the use of bone marrow transplantation where suitable facilities and compatible donors exist;[2] if transplantation is carried out before organ damage is marked, successfully transplanted patients are apparently cured and can lead a normal life.[9,10] Gene therapy is also under investigation.

An alternative approach using hydroxycarbamide in an attempt to stimulate fetal haemoglobin production and 'mop up' some of the excess α globin chains has been tried experimentally but results have been mixed. Results of an initial study in patients given butyric acid (as an arginine butyrate infusion) for the same purpose appeared more promising[11] although a subsequent study failed to show any benefit.[12] Mixed results have also been reported with the use of oral butyrate derivatives such as sodium phenylbutyrate[13] and isobutyramide.[14]

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Haemostasis and Fibrinolysis

Haemostasis is the physiological response that occurs whe blood vessels are damaged. It results in coagulatio (formation of a blood clot) and thus stops bleeding. Th initial response is the formation of a plug of platelets, whic adhere both to the injured tissue and to each other. Th vessel injury, with factors released by the platelets, trigger series of reactions (the coagulation 'cascade') mediated b proteins circulating in the plasma (blood clotting factors) This results in formation of an insoluble fibrin clot tha reinforces the initial platelet plug. Regulatory mechanism come into operation to prevent widespread coagulation Lysis of the clot (fibrinolysis) then occurs when woun healing and tissue repair are underway.

Platelet aggregation. Platelets usually circulate ir plasma in an inactive form. Contact with damage endothelium causes them to become activated and t adhere to the site of injury. This adhesion is partly mediate by binding of von Willebrand factor (factor VIII-related antigen; vWF), a plasma protein that also acts as a carrier for factor VIII, to a glycoprotein (termed GPIb) on the platelet membrane surface. Substances are secreted by the activated platelets which cause further platelet aggregation (adenosine diphosphate and thromboxane A_2) and vasoconstriction (serotonin and thromboxane A_2). Thromboxane A_2 secreted by platelets is derived from arachidonic acid.

- Adenosine diphosphate stimulates platelet activation and aggregation by its effect at $P2Y_{12}$ receptors on the platelet surface. This effect is inhibited by **antiplatelet drugs** such as clopidogrel, prasugrel, and ticlopidine, that are $P2Y_{12}$ receptor antagonists.
- The enzyme cyclo-oxygenase is required for the synthesis of thromboxane A_2 and this enzyme is inhibited by the antiplatelet drugs aspirin and sulfinpyrazone. Aspirin binds irreversibly to the enzyme and therefore the antiplatelet effect lasts for the lifetime of the platelet. Sulfinpyrazone is a reversible inhibitor of the enzyme.

Platelet aggregation involves interaction of fibrinogen with a receptor, glycoprotein IIb/IIIa, on the platelet surface.

- Antiplatelet drugs such as abciximab act by blocking this receptor.

In addition to their action in forming the initial haemostatic plug, platelets are also involved in coagulation by providing a surface on which interactions between clotting factors take place, resulting in more efficient coagulation.

Coagulation. The series of reactions that results in formation of a fibrin clot may be conveniently considered as two pathways, the *intrinsic* pathway (triggered within the blood) and the *extrinsic* pathway (triggered by substances extraneous to the blood). While this distinction is useful for understanding *in-vitro* coagulation and is the basis for tests that are specific for each pathway (see below), the mechanism of *in-vivo* coagulation is not so segregated and factors appearing in one pathway are also necessary for reactions in the other pathway. The intrinsic and extrinsic pathways of coagulation and the *in-vivo* pathways are discussed further below and are represented in summary form in Figure 1, p. 1126 and Figure 2, p. 1127, respectively. Factors circulate in the blood in an inactive form and are activated by cleavage of peptide bonds. The numerals attached to the factors reflect the order in which they were discovered and not their importance or position in the chain of reaction. The letter 'a' after a factor name or number denotes the activated form. Factors involved in blood coagulation are listed in Table 2, p. 1125. Once the coagulation cascade is started, activated factors act in positive feedback mechanisms to amplify the activation steps thus producing rapid coagulation. Cofactors are necessary as they increase the speed of the reactions. Other components necessary for coagulation are calcium ions and a membrane surface. Calcium ions are required for nearly all the reactions. Many of the activation steps, notably those involving factors VII, IX, and X, take place on a membrane surface expressing tissue factor, or platelets. Factors bind to phospholipids on the membrane surface.

The *extrinsic* pathway begins when *tissue factor* (factor III; tissue thromboplastin) is released from damaged tissue. This forms a complex with *factor VII* (proconvertin; SPCA; stable factor) and factor VIIa and directly activates *factor X* (Stuart factor; Stuart-Prower factor). The *intrinsic* pathway begins when blood comes into contact with a negatively charged surface. *Factor XII* (Hageman factor) interacts with high molecular weight kininogen (HMWK; Fitzgerald factor) and prekallikrein (Fletcher factor) to produce *kallikrein*, which activates factor XII. The active factor XIIa then activates *factor XI* (plasma thromboplastin antecedent; PTA), which in turn activates *factor IX* (Christmas factor; plasma thromboplastin component; PTC). *Factor VIII* (antihaemophilic factor; AHF) is activated by thrombin to factor VIIIa to act as a cofactor for factor IXa, which converts *factor X* to factor Xa. The extrinsic and intrinsic pathways therefore converge with the activation of factor X. *Factor V* (Ac-

globulin; labile factor; proaccelerin) is activated by thrombin to factor Va to be a cofactor for factor Xa, which converts prothrombin (*factor II*) to thrombin with the subsequent formation of a *fibrin* gel. *Factor XIII* (fibrin stabilising factor; FSF) is also activated by thrombin to factor XIIIa, which stabilises the fibrin gel to form a stable clot.

The dependence of many steps in the coagulation cascade on calcium ions (know as *factor IV*) allows coagulation *in vitro* to be blocked by the addition of calcium chelators, such as sodium citrate, to collected blood. When collected blood is tested for coagulation function, addition of calcium ions allows clotting to proceed. Tests of coagulation function include activated partial thromboplastin time (APTT), which is a measure of the activity of the intrinsic system, prothrombin time (PT), a measure of the activity of the extrinsic system, and thrombin clotting time, which measures the conversion of fibrinogen (*factor I*) to fibrin.

The factors involved in triggering the *in-vitro intrinsic* pathway, that is prekallikrein, factor XII, and possibly factor XI, are probably not important in *in-vivo* blood coagulation as deficiency of any of these factors is not associated with a serious bleeding disorder. The important step in the clotting cascade *in vivo* is release of *tissue factor* (factor III) from damaged tissue. As has already been mentioned, tissue factor forms a complex with *factor VII* and factor VIIa that activates *factor X*. Factor Xa activates *prothrombin* resulting in formation of a *fibrin clot* which occurs as described above under the *in-vitro* systems. To enhance coagulation, various positive feedback mechanisms and other clotting factors operate to increase production of activated factors VII and X. For example, formation of factor VIIa is amplified by factor VIIa itself and by factor Xa. Formation of factor Xa is amplified by factor IXa produced by the action of thrombin on factor XI.

Regulation of coagulation. The process of blood coagulation is regulated to ensure that it remains localised at the site of injury and does not result in more widespread clotting. This is achieved by dilution of clotting factors in flowing blood, by rapid hepatic clearance of many activated factors or products, and by natural anticoagulant mechanisms, which include antithrombin III, protein C, and protein S (see Figure 2, p. 1127). *Antithrombin III* (major antithrombin; AT-III; heparin cofactor) inhibits the serine protease clotting factors, that is, thrombin, IXa, Xa, XIa, and XIIa. Antithrombin III is activated by binding to glycosaminoglycans, such as heparan glycosaminoglycan and dermatan sulfate, present in vascular endothelium.

- Heparin and low-molecular-weight heparins act as **anticoagulants** by binding antithrombin III at a specific binding site and enhancing its inhibitory effect on the serine protease clotting factors. At therapeutic doses of heparin the factors inhibited are thrombin and factor Xa. Low-dose heparin, such as that given for the prophylaxis of thromboembolism, inhibits factor Xa. Very high doses of heparin have a direct inhibitory effect on antithrombin III. Heparinoids which lack the specific binding site for antithrombin III do not have the anticoagulant properties of heparin. Low-molecular-weight heparins have a higher ratio of anti-factor-Xa to antithrombin activity than heparin and therefore mainly inhibit factor Xa.

Proteins C and S are both vitamin K-dependent plasma proteins. Protein C (autoprothrombin IIA; factor XIV) circulates in plasma in an inactive form. It is activated by contact with thrombin that is bound to thrombomodulin, a receptor located on the surface of endothelial cells. Activated protein C inhibits factors Va and VIIIa and therefore slows blood clotting. Protein S acts as a cofactor in this inhibition.

Vitamin K is essential for the activities of factors II, VII, IX, and X. It is also essential for the activity of proteins C and S. These factors contain glutamic acid residues that undergo carboxylation in the liver, a reaction requiring reduced vitamin K as a cofactor. This carboxylation step allows the factors to bind calcium, a reaction necessary for their function in the clotting cascade.

- Deficiency of vitamin K or the use of **oral anticoagulants** (which are vitamin K antagonists) therefore impairs the function of these clotting factors. Oral anticoagulants have no effect on circulating clotting factors and thus the time required before the anticoagulant effect is seen depends on the individual clearance rate of the factor.

Fibrinolysis is the mechanism of clot dissolution. It is mediated by *plasminogen*, which circulates in plasma in an inactive form; conversion to its active form, *plasmin*, occurs when plasminogen binds to fibrin in the presence of a *plasminogen activator* (see Figure 2, p. 1127). Plasmin, a *proteolytic enzyme*, digests fibrin clots and hydrolyses other proteins, including factors II, V, VIII, and XII. As fibrin is lysed, plasmin is released which is inhibited by α_2-antiplasmin to prevent a systemic lytic state developing. There are two types of plasminogen activator, *tissue plasminogen activator* (tPA), which originates from the endothelium, and *urokinase*, which is activated from prourokinase. Activators of prourokinase include plasmin. Tissue plasminogen activator binds to fibrin and thus activates plasminogen bound to fibrin much more rapidly than circulating plasminogen; therefore the fibrinolytic action of tissue plasminogen activator is fibrin specific. Urokinase does not bind to fibrin, and therefore its fibrinolytic action is not fibrin specific, although it is activated by plasmin that is bound to fibrin. *In vivo*, fibrinolysis is almost entirely due to the activity of tissue plasminogen activator.

- The two types of plasminogen activator with their different modes of action provide the basis for the specificity of **thrombolytics** (the so-called 'clot specific' effect), which act by promoting the conversion of plasminogen to plasmin. The tissue plasminogen activators alteplase and tenecteplase are fibrin-specific thrombolytics, and streptokinase and urokinase are fibrin-nonspecific.
- The **antifibrinolytic drugs** aminocaproic acid and tranexamic acid act mainly by blocking the binding of plasminogen and plasmin to fibrin, thereby preventing the breakdown of fibrin clots.
- Aprotinin, an inhibitor of proteolytic enzymes, acts as a **haemostatic** by inhibiting the action of plasmin and therefore preventing the breakdown of fibrin clots. Other drugs acting as haemostatics include batroxobin, which is reported to promote the production of fibrin from fibrinogen, and etamsylate, which has a stabilising effect on the capillary wall. Drugs such as oxidised cellulose, calcium alginate, collagen, and gelatin act by providing a physical meshwork within which clotting can occur. Adrenaline, adrenalone, and noradrenaline produce haemostasis by causing vasoconstriction. Drugs with astringent properties such as alum and ferric chloride are also used for haemostasis.

The use of haemostatics may be considered when bleeding cannot be controlled by direct measures such as the application of pressure, suture or ligation, or electrocoagulation.

Dysfunction of the haemostatic mechanisms or the systems regulating haemostasis produces haemorrhagic disorders (acquired, below, and inherited p. 1128.2) or thromboembolic (p. 1273.2) disorders.

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Table 2. Proteins involved in blood coagulation and in fibrinolysis.

	Proteins	Synonyms
Blood coagulation	Factor I	Fibrinogen
	Factor II*	Prothrombin
	Factor III	Tissue thromboplastin; tissue factor
	Factor IV	Calcium ion
	Factor V	Ac-globulin; labile factor; proaccelerin
	Factor VI (unassigned)	
	Factor VII*	Proconvertin; SPCA; stable factor
	Factor VIII	Antihaemophilic factor; AHF
	Factor IX*	Christmas factor; plasma thromboplastin component; PTC
	Factor X*	Stuart factor; Stuart-Prower factor
	Factor XI	Plasma thromboplastin antecedent; PTA
	Factor XII	Hageman factor
	Factor XIII	Fibrin stabilising factor; FSF
	von Willebrand factor	Factor VIII-related antigen; vWF
	High molecular weight kininogen	HMWK; Fitzgerald factor
	Prekallikrein	Fletcher factor
Fibrinolysis	Plasminogen	
	Prourokinase	
	Tissue plasminogen activator	tPA
	Antithrombin III	Major antithrombin; AT-III; Heparin cofactor
	Protein C*	Autoprothrombin IIA; Factor XIV
	Protein S*	
	α_2-Antiplasmin	

* denotes vitamin K-dependent factor

Acquired haemorrhagic disorders

Bleeding disorders sometimes arise due to disturbances in either clotting factors or platelets, or to vascular wall defects occurring as a result of a disease or a medical or surgical procedure. Disturbances and defects may also be drug-induced. In some conditions, including renal and liver disease, cardiopulmonary bypass procedures, or following massive blood transfusion, disturbances in many of the homoeostatic mechanisms occur simultaneously producing complex haemorrhagic disorders, sometimes referred to as complex acquired coagulopathies.

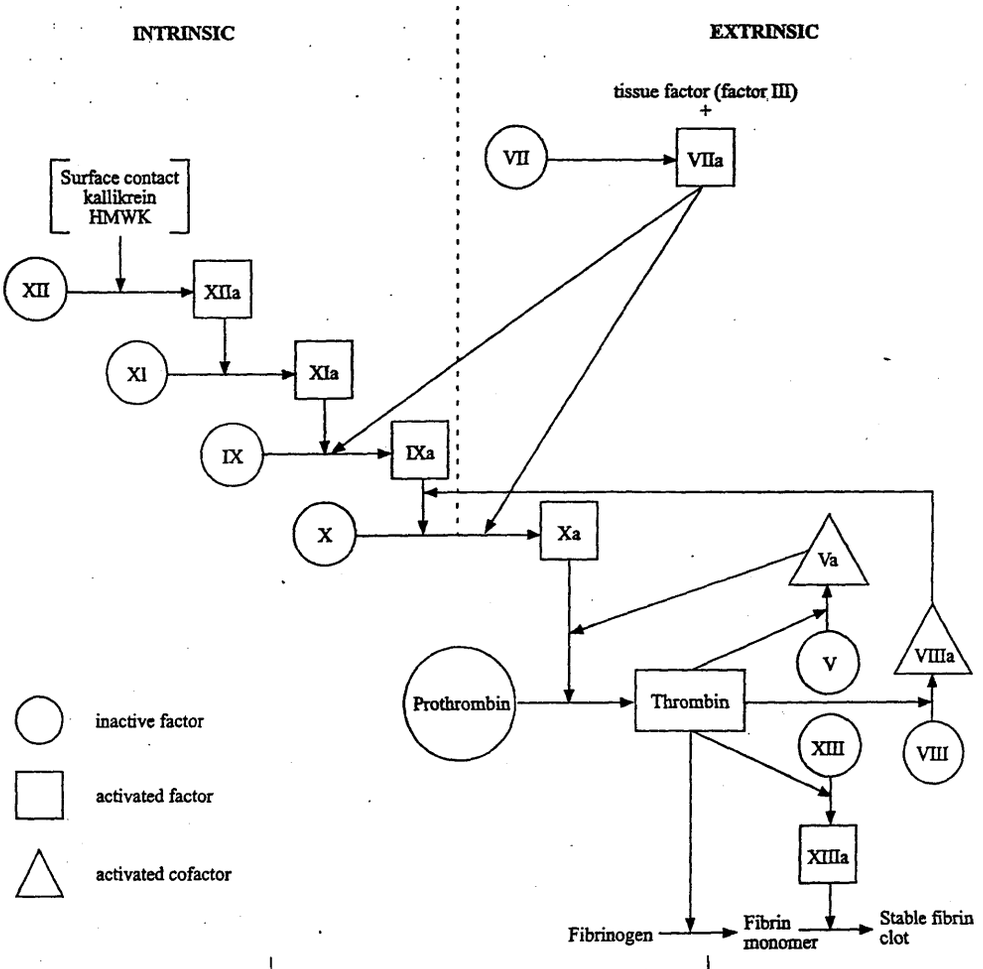
One of the commoner causes of haemorrhagic disorder caused by *disturbance of clotting factors* is overdose with heparin, oral anticoagulants, or thrombolytics. Different approaches are used in the management of overdose with these drugs, as discussed in Treatment of Adverse Effects under Heparin (p. 1399.3), Warfarin Sodium (p. 1529.1), and Streptokinase (p. 1506.3).

Deficiencies in clotting factors may occur in several diseases. Vitamin K is essential for the activity of several clotting factors and plasma proteins (see Haemostasis and Fibrinolysis, p. 1124.3), and disorders that cause a deficiency of vitamin K can lead to impairment of these. Diseases of the small bowel and biliary tract can impair absorption of vitamin K, and liver disease reduces the production of clotting factors. Deficiency is generally treated by giving vitamin K, although this is not always effective in patients with liver diseases. Vitamin K is widely used for the prevention and treatment of neonatal vitamin K deficiency bleeding (p. 2123.2). Examples of other acquired disorders that affect clotting factors but occur rarely include acquired haemophilia affecting factor VIII (see Haemophilias, p. 1126.3) and von Willebrand syndrome (see von Willebrand's Disease, p. 1129.3).

Low platelet concentrations can be associated with many other illnesses and increase the risk of bleeding; management is discussed in Thrombocytopenia, p. 1129.2.

Various drugs are used, or are under investigation, for their effect on *perioperative blood loss*.[1-4] Topical treatments such as fibrin glue, gelatin-based films and sponges, oxidised cellulose, and thrombin are used for a local haemostatic effect in surgical procedures. The antifibrinolytic drugs aprotinin; aminocaproic acid, and tranexamic acid are used to reduce bleeding and transfusion requirements in procedures such as liver transplantation and cardiac surgery involving cardiopulmonary bypass. Desmopressin is used in surgical patients with some congenital and acquired bleeding disorders, but in patients without pre-existing bleeding disorders it has not consistently been shown to be of benefit. Recombinant activated factor VII (eptacog alfa) is used in the management of bleeding in patients with

Figure 1. Simplified representation of *in-vitro* coagulation.



haemophilia, but it is also under investigation in surgical patients with normal haemostasis.

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Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is an acute or chronic syndrome resulting from an underlying condition that causes pathological stimulation of coagulation at some point in the coagulation pathway (see Haemostasis and Fibrinolysis, p. 1124.3); thrombin generation triggered by uncontrolled tissue factor is probably the main factor in most cases. Causes include obstetric emergencies (placental abruption, amniotic fluid embolism), infection (bacterial septicaemia, viraemia), neoplasms, trauma (head injury, burns), venomous snake bites, transfusion of incompatible blood, liver disease, and various vascular causes.

Stimulation of coagulation leads to microvascular thrombosis that produces widespread tissue ischaemia and may lead to ischaemia of major organs. Simultaneously, secondary activation of the fibrinolytic system and consumption of coagulation factors produces bleeding, which is often the predominant manifestation. Symptoms are therefore very variable and include those of bleeding, such as spontaneous bruising, prolonged bleeding from intravenous puncture sites, and gastrointestinal and pulmonary haemorrhage, and those of thrombosis, such as acute renal failure, venous thromboembolism, skin necrosis, liver failure, cerebral infarction, acute respiratory distress, and coma. Some cases may be asymptomatic.

Treatment of DIC is aimed mainly at the underlying cause since the condition will not resolve until the underlying trigger is removed. Recovery is often fairly rapid once treatment is started. Supportive therapy to ensure adequate hydration and tissue oxygenation is also vital. These measures may be sufficient in patients with asymptomatic DIC. Most patients with symptomatic DIC also require therapy with plasma and platelets to replace coagulation factors and arrest bleeding. Coagulation factor concentrates such as fibrinogen concentrate or cryoprecipitate are not favoured, as they do not contain all coagulation factors and they may be contaminated with traces of activated coagulation factors, which can exacerbate the coagulation disorder in these patients. Nevertheless, they may be considered in patients with fluid overload because they are available in smaller volumes, and may be useful in severe hypofibrinogenaemia that persists despite plasma replacement. Heparin has been used in the management of DIC with the aim of switching off the coagulatory mechanisms. Although benefit has been shown with some underlying causes, heparin may worsen bleeding and its use in DIC is considered by some to be controversial. Where the risk of bleeding is relatively minor and thrombosis predominates, heparin may be appropriate. Other measures that have been tried in limited numbers of patients include use of a low-molecular-weight heparin. Prophylactic doses of heparin or low-molecular-weight heparin may be used to prevent venous thromboembolism in critically ill patients who are not bleeding. Concentrates of activated protein C have been used in DIC associated with severe sepsis and have improved coagulation abnormalities and mortality. The recombinant form, drotrecogin alfa (activated), has also been used, but provided no survival benefit in patients with severe sepsis and septic shock. Antithrombin III has also been used, but despite beneficial reports of use in sepsis-related DIC a large study found no benefit.

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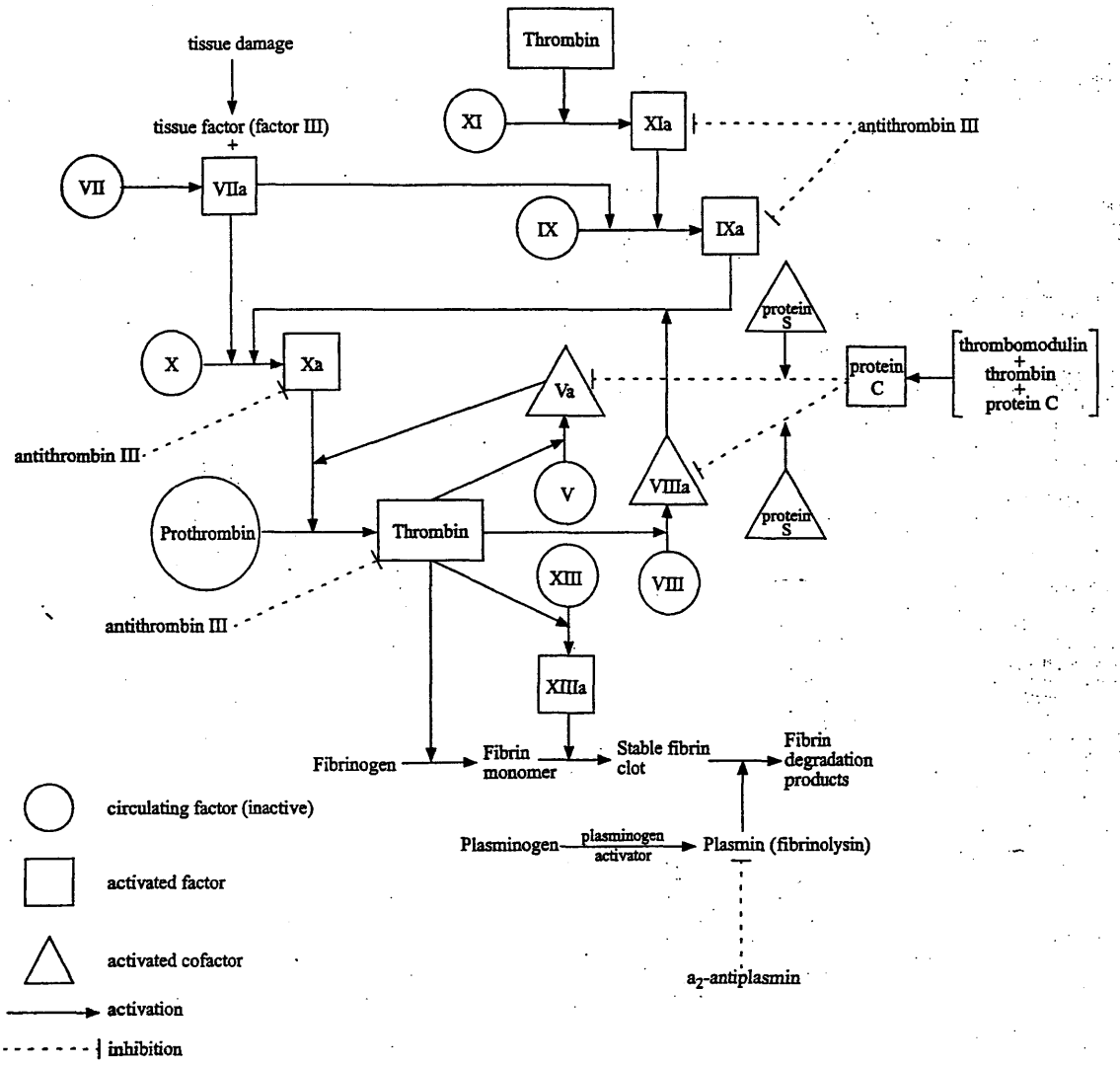
Haemophilias

The haemophilias are bleeding disorders caused by low concentrations of specific coagulation factors. Acquired haemophilia is rare and most patients have inherited forms. The most well known are haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency). Factor XI deficiency, originally called haemophilia C, is mentioned under Inherited Haemorrhagic Disorders, p. 1128.2.

Haemophilia A (classical haemophilia, factor VIII deficiency) is the most common of the serious hereditary bleeding disorders.[1] It is an X-linked recessive disorder and therefore, with rare exceptions, males are affected and females are carriers. The condition is due to deficiency of factor VIII and severity of bleeding is related to the residual factor level. The condition is severe when there is less than 1% of normal factor VIII activity, moderate when the factor VIII concentration is 1 to 5% of normal, and mild when the factor concentration is greater than 5%. Clots are slow to form and break up easily, and bleeding after trauma or surgery may be prolonged. In moderate and severe haemophilia A bleeding may occur into major joints producing long-term joint destruction, a major cause of morbidity in haemophilia. Other frequent sites of bleeding are large muscles, and renal and intestinal tracts. CNS haemorrhage may also occur, especially after trauma.

Figure 2. Simplified representation of *in-vivo* coagulation and fibrinolysis.



Treatment of bleeding episodes depends on the severity of the haemophilia.[1-4] Patients with moderate to mild haemophilia A can be satisfactorily treated with desmopressin,[5,6] which produces an increase in factor VIII and von Willebrand factor, and increases platelet adhesion and expression of tissue factor. Desmopressin also transiently stimulates plasma fibrinolytic activity, and it has been suggested that use with an antifibrinolytic, such as tranexamic acid, may inhibit this effect. However, there is no evidence for haemostatic improvement with this combination, although tranexamic acid itself is effective in the management of mucosal bleeding and during dental surgery.[3] Desmopressin is usually given intravenously. The subcutaneous route is an alternative but the maximum effect is slower. It can also be given intranasally, and this route is used by patients to treat themselves outside hospital. In patients with more severe haemophilia A, desmopressin is ineffective and treatment of bleeding episodes requires replacement of factor VIII. The amount given depends on the severity of bleeding.

Desmopressin and factor VIII preparations are also used for the *prevention of bleeding episodes* in situations where haemorrhage may be anticipated, for example before surgery or dental treatment;[7,8] patients with haemophilia A should also not be given intramuscular injections (because of potential muscle damage and bleeding into muscle) unless they are given during a period when the patient is covered by replacement factor. Prophylactic cover with an antifibrinolytic, such as tranexamic acid given orally (or, in dentistry, also topically as a mouthwash), may also be used and should be continued for 5 to 7 days after the procedure. Fibrin glue can also be useful in the control of local bleeding.[8]

An alternative method of management has been practised in Sweden since 1958 where *continuous prophylaxis* with factor VIII is given to patients with severe haemophilia A with the aim of preventing arthropathy. Therapy is started at 1 to 2 years of age and the factor VIII concentration is maintained at a level of at least 1% of normal. Patients who began receiving prophylaxis before the age of 2 have had almost no bleeding episodes and joints have remained normal for up to 16 years of follow-up.[9,10] This approach has subsequently been adopted in other countries, but regimens have varied in terms of the threshold specified for the introduction of prophylaxis, the dose of factor VIII used, and outcome measures.[11,12] Information has been mainly provided by observational studies, but a randomised controlled study[13] found less joint damage and fewer joint and other haemorrhages at 6 years of age in boys who had been given regular factor VIII prophylaxis compared with episodic treatment given only for clinically recognised joint haemorrhage. Prophylaxis is generally continued through adolescence to adulthood; about 30% of young adults are able to stop regular prophylaxis and can be adequately managed with intermittent prophylaxis tailored to specific activities, such as sports and other potentially traumatic events.[12]

There are various factor VIII preparations available that vary in activity and source.[4] Most products were previously derived from pooled donor plasma and were associated with transmission of viruses including HIV (leading to the subsequent development of AIDS), hepatitis B, and other hepatitis viruses. The introduction of products treated with heat or chemicals, and efforts to screen the donor material from which factor VIII is obtained, seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses such as human parvovirus B19 and hepatitis A may still be transmitted. It is recommended that patients not already immune should be vaccinated against hepatitis A and B. There is some concern that variant Creutzfeldt-Jakob disease (vCJD) may be transmitted by plasma-derived clotting factor products, but there is no proof as yet that this has occurred. Factor VIII produced by recombinant DNA technology may avoid the dangers of possible viral transmission and is therefore the factor VIII preparation of choice (but see also Transmission of Infections under Factor VIII, p. 1149.1). It has been suggested that high-purity plasma-derived factor VIII preparations slow the decline in CD4 count in haemophiliac patients who are HIV-positive, but this was based on the measurement of surrogate markers and the purity of clotting factor preparations has been found not to affect the development of AIDS. Factor VIII preparations are usually given by bolus injection, but there is increasing interest in the use of continuous infusion[2,11] because it can maintain a steady state of clotting factor concentrations and reduce the amount of concentrate used. Evidence from controlled studies is needed to confirm the perceived benefits of this method.

A serious complication of replacement therapy in haemophilia A is the development of *antibodies to factor VIII* (often called inhibitors). The reported incidence varies widely, up to about 30%. Antibodies are more likely to develop in young patients with severe haemophilia who receive continuous prophylaxis, but can also arise in patients with mild haemophilia, typically after intensive replacement therapy; some patients appear to have a genetic predisposition.[14] Antibody concentrations can be measured and may be classified as either low-titre or high-

titre; patients are further described as low or high responders according to the increase in antibody production when given factor VIII.[15]

The management of acute bleeding episodes can be problematic in these patients, and depends on the characteristics of the antibodies.[14-16] Patients with low-titre low-responding antibodies are generally treated with high-dose factor VIII. Porcine factor VIII may be useful in high-titre or highly-responding patients at least in the short term, although with longer use antibodies to the porcine material can develop in turn. (The manufacture of porcine factor VIII was discontinued in 2004, but a recombinant product is in development.) Otherwise, when high-titre highly-responding antibodies are present, bleeding episodes are managed with factor VIII inhibitor bypassing fraction, or recombinant factor VIIa, which bypass the factor VIII-dependent step in the coagulation cascade. The removal of antibodies by plasmapheresis, with or without extracorporeal immunoadsorption, followed by high-dose factor VIII, has been used in high-titre patients when other measures have failed.[16]

Attempts have been made to induce tolerance and eradicate the antibodies.[14,15,17] Regimens have used regular doses of factor VIII over prolonged periods, sometimes with immunosuppression by cyclophosphamide, immunomodulation by normal immunoglobulin, or extracorporeal immunoadsorption. The treatment of bleeding episodes during immune tolerance induction therapy can be difficult, requiring the use of factor VIII inhibitor bypassing fraction or recombinant factor VIIa.

A future development that may provide a clinical cure for haemophilia is *gene therapy*.[1,18,19] However, despite successful treatment in *animal* models, initial human studies for haemophilia A and B have shown no sustained responses.

Haemophilia B (factor IX deficiency; Christmas disease) is less common than haemophilia A. The classification and clinical features of this form are the same as for haemophilia A, but are related to a deficiency of factor IX. Treatment follows the same principles as for haemophilia A,[1-4] except that desmopressin does not affect factor IX concentrations and is therefore ineffective in haemophilia B. Bleeding episodes are treated with factor IX replacement, preferably using recombinant factor IX or plasma-derived highly purified factor IX preparations that do not contain other clotting factors. Low-purity factor IX preparations derived from plasma that contain other clotting factors in addition to factor IX (prothrombin complex concentrates) are associated with thromboembolic complications, particularly in patients with liver disease and others at increased risk of thromboembolism or disseminated intravascular coagulation. Fresh frozen plasma may be used in emergencies if specific factor IX products are unavailable. Antifibrinolytic drugs may be used in patients treated with purified factor IX preparations,[3] but should be avoided in those given prothrombin complex concentrates because of the increased risk of thrombosis. Continuous prophylaxis using factor IX preparations has also been used in haemophilia B.[9,10] As in patients with haemophilia A, vaccination against hepatitis A and hepatitis B is recommended for all haemophiliacs not already immune.

Antibody inhibitors of factor IX can be produced although the incidence of antibody formation is lower than that seen in haemophilia A. Acute bleeding episodes in these patients may be managed using recombinant factor VIIa.[3] Induction of tolerance has also been used for antibodies in haemophilia B, but the response is not as good as for haemophilia A and these patients appear to be at risk of anaphylaxis and nephrotic syndrome.[3,14]

As mentioned under haemophilia A, gene therapy is under investigation as a possible clinical cure.

Acquired haemophilia is a rare disease in which autoantibodies form against factor VIII.[20,21] In about 50% of cases, factor VIII autoantibodies are idiopathic; the rest are associated with other conditions including the postpartum period, malignancies, auto-immune diseases, and adverse drug reactions. The bleeding pattern is different to congenital haemophilia and usually occurs as bleeding in the skin or muscles, haematuria, haematemesis or melaena, and prolonged postpartum or postoperative bleeding; haemarthroses are relatively uncommon.

Treatment for acute episodes depends on the severity of bleeding and the antibody titre. Desmopressin is only effective in patients with low inhibitor titres. Large doses of plasma-derived or recombinant factor VIII may be effective, but the dose required to saturate the autoantibodies can be difficult to predict and therapy must be closely monitored to adjust dosage according to factor VIII concentrations. The use of porcine factor VIII concentrate is an alternative. Increasingly, patients are being managed with factor VIII inhibitor bypassing fraction or recombinant factor VIIa, and these may be used when the titre is very high or bleeding persists despite the use of factor VIII concentrates.

Up to a third of patients with acquired haemophilia have a spontaneous resolution of their autoantibodies. For other patients, treatment to eradicate or suppress the autoantibodies is often based on a corticosteroid, such as prednisone, given alone or combined with cyclophosphamide; evidence for the efficacy of such treatment is largely anecdotal however. Other combinations that have also been tried include a corticosteroid with azathioprine, or a corticosteroid with cyclophosphamide plus vincristine. Ciclosporin, alone or with a corticosteroid, has been used as a salvage therapy. Rituximab has produced durable responses, when used alone or with immunosuppressive therapy, in a small number of patients. Intravenous immunoglobulin has been tried, but any benefit is questionable. Similarly, plasmapheresis and immunoadsorption have been used, but their contribution to the success of treatment is difficult to assess because they are usually combined with immunosuppressive drug therapy. Factor VIII immune tolerance regimens are rarely, if ever, used in acquired haemophilia.

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Inherited haemorrhagic disorders

Inherited disorders that lead to abnormal bleeding include platelet disorders and disturbances in clotting factors.

Inherited platelet disorders can affect platelet function, size, and number. Platelet function disorders include abnormalities in platelet receptors (such as Glanzmann's thrombasthenia), platelet granules (storage pool deficiencies), signal transduction pathways and granule release, and membrane phospholipids.[1,2] Treatment depends on the disorder, but in some conditions desmopressin or platelet transfusions are useful in the management of bleeding.[2] Inherited thrombocytopenias are discussed under Thrombocytopenia, p. 1129.2.

Inherited disorders that result in deficiencies or abnormalities of clotting factors can cause variable degrees of bleeding. The most common inherited disorders of clotting factors are haemophilias A and B (p. 1126.3) and von Willebrand disease (p. 1129.3). Other inherited disorders are rare[3] but include abnormalities of fibrinogen, deficiencies of the individual factors II, V, VII, X, XI (haemophilia C), XIII, and combined deficiencies of factors V and VIII, or of factors II, VII, IX, and X. Management depends on the clotting factors affected and the degree or risk of bleeding. In general, antifibrinolytics such as tranexamic acid may be adequate for control of mucosal bleeding and menorrhagia, and fibrin glue may be useful for local haemostasis. Severe bleeding requires the replacement of clotting factors, preferably using specific factor concentrates or recombinant factor products; fresh frozen plasma may be a suitable alternative when more specific products are not available. Vitamin K treatment may be considered in patients with deficiencies of vitamin K-dependent clotting factors (II, VII, IX, and X).

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Neonatal intraventricular haemorrhage

Intraventricular haemorrhage, also referred to as periventricular or periventricular-intraventricular haemorrhage, is bleeding from vessels in or around the ventricles of the brain. It is the major cause of death in very low birth-weight neonates and can affect up to 60% of neonates weighing less than 1500 g. Intraventricular haemorrhage is rare in neonates over 32 weeks of gestation, since the vessels that bleed involute early in the third trimester. Intraventricular haemorrhage usually develops within the first 3 days of life. The haemorrhage may be graded from 1 to 4 according to severity, the higher numbered grades being the most severe and most likely to produce the long-term consequences of impaired motor and mental function. The aetiology is probably multifactorial and may include fluctuations in cerebral blood flow due to failure of autoregulatory mechanisms and tissue damage caused by oxygen free-radicals.

Once intraventricular haemorrhage has occurred treatment is supportive and includes correction of anaemia, hypotension, and acidaemia, and management of raised intracranial pressure.

As intraventricular haemorrhage is a major risk factor for impaired motor and mental development prevention is very important. Many interventions aim to reduce its incidence and include prevention of premature births, avoidance of hypercapnia, correction of major haemodynamic disturbances, and correction of coagulation abnormalities. Various drugs have also been tried including corticosteroids, etamsylate, indometacin, pancuronium, phenobarbital, vitamin E, and vitamin K. Some of these drugs have been given to the mother antenatally since the development of intraventricular haemorrhage may be related to perinatal events.

- Giving corticosteroids to pregnant women at risk of preterm delivery is recommended to prevent neonatal respiratory distress syndrome (p. 1608.3) and may also reduce the incidence of intraventricular haemorrhage.[1] A review of data from 12 controlled studies involving antenatal corticosteroid use (mainly to prevent respiratory distress syndrome)[2] suggested that the risk of intraventricular haemorrhage was also reduced but this was based on limited data. Further studies[3-6] have supported this finding, although few have involved randomised doses of corticosteroids. The mechanism for the beneficial effect of corticosteroids is not clear but avoidance of neonatal hypotension has been suggested.[3]
- Etamsylate limits capillary bleeding through its action on hyaluronic acid and initial studies showed a reduction in intraventricular haemorrhage. A subsequent study[7] showed little evidence of benefit on short-term follow-up, although confidence intervals were wide. Follow-up[8] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Follow-up of another study[9] also found that despite a reported reduction in intraventricular haemorrhage with etamsylate, developmental outcome assessments at about 4 years of age showed that it had not reduced cerebral palsy compared with the control group.
- Indometacin may reduce cerebral blood flow as a result of vasoconstriction, reduce oxygen free-radical damage, and accelerate maturation of blood vessels around the ventricles. Early studies produced conflicting results but a later larger multicentre study[10] showed a reduction in both incidence and severity although there was an unusually large number of neonates with severe intraventricular haemorrhage in the control group.[11] A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps.[11] However, follow-up of the infants included in the multicentre study at the ages of 3 years,[12] 4.5 years,[13] and 8 years,[14] reported no adverse effects on cognitive or motor development. Further

analysis of the data from this cohort has suggested that indometacin may reduce intraventricular haemorrhage in boys but have little effect in girls;[15] a true difference in effect between the sexes remains to be confirmed however. Another large multicentre study[16] also found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[17] concluded that although indometacin prophylaxis reduced the rate of severe intraventricular haemorrhage, it did not improve the rate of survival free of neurosensory disability.

- Neuromuscular blockers, such as pancuronium, abolish non-synchronous respiration and therefore stabilise both cerebral and arterial blood flow velocity and some studies have shown a reduction in intraventricular haemorrhage in mechanically ventilated neonates (see Intensive Care, p. 2028.3). However, other studies have produced conflicting results and routine use in all ventilated neonates is not recommended.
- Phenobarbital was also suggested to act by stabilising fluctuations in cerebral blood flow, and studies of use in neonates show similarly inconsistent results with many showing no benefit. A meta-analysis[18] concluded that postnatal phenobarbital could not be recommended as prophylaxis, and was associated with an increased need for mechanical ventilation. Initial studies of antenatal phenobarbital were more promising with a decrease in severity of haemorrhage being reported.[19] However, a larger randomised study[20] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants who could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[21] A concern with the use of phenobarbital in the perinatal period is that it may lower Apgar scores and produce respiratory depression. A meta-analysis[22] did not support the maternal use of phenobarbital.
- Vitamin E protects polyunsaturated fatty acids, and thus membranes, from oxidation. As oxygen free-radical damage may contribute to the development of intraventricular haemorrhage, vitamin E may have a role in its prevention. Results have been conflicting. A systematic review[23] of studies in preterm infants (gestational age less than 37 weeks or birth-weight less than 2500 g) found that vitamin E reduced the risk of intraventricular haemorrhage overall, but only reduced the risk of severe haemorrhage in surviving very low birth-weight infants (less than 1000 g). There was also a suggestion that intravenous vitamin E may have no effect compared with other dosage routes. However, the strength of these findings is limited and there was an increased risk of sepsis associated with vitamin E use, such that the role of supplementation with this vitamin has not been established in preterm infants.
- The activity of vitamin K-dependent coagulation factors is reduced in neonates and antenatal vitamin K in mothers has been tried as a means of preventing intraventricular haemorrhage. However, results of studies have not been promising. Most studies have been too small to produce conclusive results and a larger randomised controlled study[24] in 139 mothers failed to find any benefit from vitamin K prophylaxis. A subsequent systematic review[25] of 7 studies, including this one, also concluded that antenatal vitamin K use did not prevent intraventricular haemorrhage in preterm infants.

Plasma volume expansion using fresh frozen plasma or a plasma substitute has also been thought to reduce intraventricular haemorrhage by stabilising the circulation, but a prospective multicentre study found no evidence of reduction in haemorrhage[26] or subsequent death and disability[27] after the use of plasma or gelatin as volume expanders.

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Thrombocytopenia

Platelet concentrations in healthy individuals range from 150×10^9 cells/litre to 450×10^9 cells/litre, and thrombocytopenia is often **defined** as a reduction in the number of circulating platelets to less than 150×10^9 cells/litre (150 000 cells/mm^3). As the platelet count falls the risk of bleeding increases, although spontaneous bleeding is uncommon unless the count falls below 10×10^9 cells/litre to 20×10^9 cells/litre, or there is an abnormality in platelet function. Thrombocytopenia can result from decreased production, increased destruction, or abnormal splenic sequestration of platelets.

There are several **congenital forms** of thrombocytopenia that can affect platelet size, number, and function. They range across a wide clinical spectrum from mild forms, which may only be discovered incidentally and do not require specific treatment, to severe forms that are associated with a high risk of bleeding and may ultimately require haematopoietic stem cell transplantation.[1]

Secondary thrombocytopenia can be associated with many other illnesses.[2] Decreased platelet production may occur in bone marrow diseases such as leukaemias and aplastic anaemia, some viral illnesses, chronic alcohol toxicity, and liver disease. Increased destruction of platelets occurs in many disorders including immune thrombocytopenia (p. 1606.1), sepsis, disseminated intravascular coagulation (p. 1126.1), and thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p. 1159.1). Gestational thrombocytopenia[3] is a mild form that usually occurs in late pregnancy, in which platelet concentrations return to normal within 12 weeks after delivery. More severe thrombocytopenia may be caused by obstetric conditions including pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. Neonatal thrombocytopenia[4] that is mild and of early onset (in the first 72 hours of life) may be secondary to placental insufficiency and reduced platelet production. More severe thrombocytopenia of later onset may result from platelet destruction associated with sepsis or necrotising enterocolitis. In neonatal allo-immune thrombocytopenia, maternal antibodies against fetal platelet antigens cross the placenta to cause disease ranging from mild self-limiting thrombocytopenia to neonatal intracranial haemorrhage. In neonatal auto-immune thrombocytopenia there is placental transfer of maternal platelet autoantibodies in mothers with conditions such as idiopathic thrombocytopenic purpura or SLE.

Drug-induced thrombocytopenia has been reported with many drugs.[5–9] Decreased platelet production can be caused by drugs that have a toxic effect on bone marrow, including many antineoplastics. Drugs that are often implicated in immune-mediated platelet destruction include anticonvulsants, cinchona alkaloid derivatives (quinine, quinidine), diuretics, disease-modifying antirheumatic drugs (penicillamine, gold salts), NSAIDs, and sulfonamides. The 2 types of heparin-induced thrombocytopenia have been well documented (see p. 1399.1).

Treatment of thrombocytopenia is based on management of the underlying disorder where appropriate, or stopping the offending drug. Platelet infusions are used in the treatment of active bleeding or in thrombocytopenic patients who are at risk of bleeding. They should not be used when there is a thrombotic process such as in thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia. The platelet count at which infusion may be considered depends on various factors including the cause of thrombocytopenia, the presence of additional risk factors such as sepsis, the degree of bleeding, and whether the risk is related to surgery. For example, if there is active bleeding or invasive procedures are contemplated, platelet infusion may be used when the count is less than 50×10^9 cells/litre. In patients with no bleeding and no additional risk factors, a lower threshold of 5×10^9 cells/litre may be adequate.[2,10] Patients requiring long-term treatment may develop antibodies to HLA with repeated transfusions from random donors, which results in impaired responsiveness to subsequent transfusion; these patients should receive platelets obtained from a single donor for each transfusion, preferably HLA-matched.[2,10] In platelet refractoriness, when thrombocytopenia is a result of non-immune platelet destruction, treatment is problematic and although prophylactic platelet infusions may be given, it is unknown whether this is effective.[10]

Oprelvekin (recombinant human interleukin-11) is a platelet growth factor that has recently been introduced for the prevention of severe antineoplastic-induced thrombocytopenia. Romiplostim and eltrombopag, both thrombopoietin receptor agonists, have been developed for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia. Recombinant human thrombopoietin is also under investigation.

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von Willebrand's disease

von Willebrand's disease (vWD)[1–3] is a congenital bleeding disorder caused by a deficiency or dysfunction of von Willebrand factor (vWF), a plasma protein that stimulates platelet aggregation and acts as a carrier for factor VIII to protect it from premature destruction. There is also a secondary deficiency of factor VIII, because of its dependence on vWF. There are 3 main phenotypes of vWD:

- type 1 is the most common and is characterised by mild to moderate deficiencies of vWF and factor VIII
- type 2 results in qualitative abnormalities of vWF, and is further divided into subtypes according to the defect
- type 3 is rare but is a severe bleeding disorder due to very low or undetectable plasma levels of vWF, with low but usually detectable concentrations of factor VIII.

The clinical presentation of vWD includes easy bruising and bleeding from mucosal surfaces, such as epistaxis; severely affected patients may have spontaneous soft-tissue bleeding resulting in haematomas and haemarthroses. Excessive and prolonged bleeding can occur after surgery, and women may have excessive bleeding during menstruation and childbirth.[1-3]

Patients are usually only treated at the time of spontaneous bleeding or given prophylaxis before invasive procedures. Desmopressin transiently increases both vWF and factor VIII levels and is used in patients with type 1 disease. It is less likely to be effective in type 2 disease where vWF is dysfunctional. It is generally contra-indicated in type

2B disease because the abnormal vWF that is released may induce platelet aggregation and thrombocytopenia, although this is usually transient and often not associated with bleeding or thrombosis. Type 3 disease does not respond to desmopressin because of the lack of vWF stores.[1-3]

Plasma concentrates that contain both vWF and factor VIII are used when desmopressin is not suitable. A concentrate that contains highly purified vWF, with very little factor VIII, is available in some countries. Very highly purified factor VIII preparations, or recombinant forms, should not be used; they do not contain appreciable amounts of vWF so the factor VIII therefore has a very short half-life, making it ineffective (but see also below, about the management of patients with alloantibodies). When haemorrhage is not controlled despite adequate factor VIII levels, platelet concentrates may be required.[1-3] Cryoprecipitate may be used as a source of clotting factors and vWF when other measures have failed, or in serious situations when vWF concentrates are not available, but it does not consistently correct bleeding time and has a higher risk of transfusion-transmitted infection.[2,3]

Some patients with type 3 disease who have received multiple transfusions develop alloantibodies that inactivate vWF and form circulating immune complexes. Further use of concentrates that contain vWF is contra-indicated because of the risk of anaphylaxis. There are a few reports of successful control of surgical bleeding in such patients by continuous infusion of recombinant forms of factor VIII and activated factor VII, which contain no vWF.[1,2]

Antifibrinolytic drugs, such as tranexamic acid or aminocaproic acid, may be sufficient in the management of less severe forms of mucosal bleeding, and are used as adjuncts to desmopressin or plasma concentrates in patients undergoing surgery.[1-3] Fibrin glue or bovine thrombin may also be used as topical adjuncts for oral surgery.[3] Hormonal contraceptives can reduce bleeding in women with vWD and menorrhagia.[1-3]

Acquired von Willebrand syndrome is rare, and is usually associated with conditions such as lymphoproliferative and myeloproliferative diseases, cancers, auto-immune diseases, and hypothyroidism. Some drugs have been reported to cause an acquired von Willebrand syndrome, including ciprofloxacin and valproic acid. Depending on the underlying cause, vWF activity may be affected by accelerated clearance, reduced synthesis, or an inhibition of function. Management is based on treatment of the underlying cause, but specific options for treatment of bleeding include desmopressin, factor concentrates, and intravenous immunoglobulin.[1-4] Plasma exchange and extracorporeal immunoadsorption have also been used successfully.[2,4]

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Neutropenia

A circulating neutrophil count below 1.5×10^9 cells/litre (1500 cells/mm^3) is usually regarded as abnormal and neutrophil counts below 0.5×10^9 cells/litre are associated with increased risk of infections. Neutropenia may be a result of reduced production, increased peripheral destruction, or increased peripheral pooling of neutrophils, and can be inherited or acquired.

Inherited forms of neutropenia are rare and include congenital agranulocytosis (Kostmann's syndrome: severe persistent neutropenia with frequent and severe infections that start in infancy) and cyclic neutropenia (fluctuating periods of neutropenia accompanied by fever, mouth ulceration, and serious infection).

Granulocyte colony-stimulating factors have been shown to reduce the incidence of severe infections and have improved substantially the quality of life of patients with congenital neutropenias although there are some concerns over their safety. As patients survive longer with such treatment they show an increased risk of developing myelodysplastic syndrome and leukaemia. However, it is unclear whether prolonged survival unmasks the natural course of the disease or whether granulocyte colony-stimulating factor further increases the risk of leukaemic transformation. Haematopoietic stem cell transplantation may be indicated for patients whose disease is refractory to colony-stimulating therapy or has transformed into myelodysplastic syndrome or leukaemia. Cyclic neutropenia is also managed with granulocyte colony-stimulating factor, but leukaemic transformation does not seem to occur in these patients.

There are many causes of **acquired** neutropenia. Drugs are a common cause, either by direct toxicity to the bone marrow, or by immune-mediated marrow suppression or peripheral destruction. Drugs that cause dose-related direct toxicity include cytotoxic and immunosuppressive drugs, flucytosine, ganciclovir, and zidovudine. Drugs that appear to cause neutropenia by immune-mediated mechanisms include sulfur-containing drugs (such as captopril, co-trimoxazole, and some antithyroid drugs), clozapine, penicillins, and cephalosporins. Patients with drug-induced neutropenia usually present with fever of sudden onset, sore throat, mouth ulcers, headache, and malaise. This condition is also known as **agranulocytosis**. Other causes of acquired neutropenia include serious bacterial and viral infections, radiotherapy, neoplasms that invade bone marrow, and some auto-immune disorders.

The management of acquired neutropenia includes the treatment of any contributory condition. Drug-induced neutropenia is usually managed by withdrawal of the offending drug. After an idiosyncratic reaction the implicated drug should not be given again, since abrupt neutropenia will usually be precipitated. Colony-stimulating factors can be used to manage drug-induced neutropenia.

In all neutropenic patients onset of fever is indicative of serious infection and is treated immediately with empirical antibacterial therapy, as described under Infections in Immunocompromised Patients, p. 186.3.

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Albumin ⊗

Albümin; Albúmina; Albumine; Albuminlösung vom Menschen; Albuminum.

ATC — B05AA01.

ATC Vet — QB05AA01; QV08DA01 (microspheres of human albumin).

UNII — 27432CM55Q (bovine albumin); B05Y6V2CZS (egg albumin); ZIF514RVZR (human albumin).

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii) and *US.*

USNF includes a solution of a recombinant human albumin.

Ph. Eur. 8: (Human Albumin Solution; Albumini Humani Solutio). A sterile liquid preparation of a plasma protein fraction containing human albumin obtained from the plasma of healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. It is prepared as a concentrated solution containing 15 to 25% of total protein or as an isotonic solution containing 3.5 to 5% of total protein; not less than 95% of the total protein is albumin. A suitable stabiliser, such as sodium octanoate or *N*-acetyltryptophan or a combination of the two, may be added but no antimicrobial preservative or antibiotic is added. It contains not more than 160 mmol of sodium per litre and not more than 200 micrograms of aluminium per litre. The solution is sterilised by filtration and distributed aseptically into containers which are sealed to prevent contamination and maintained at 59 degrees to 61 degrees for not less than 10 hours. Finally, the containers are incubated for not less than 14 days at 30 degrees to 32 degrees or for not less than 4 weeks at 20 degrees to 25 degrees and examined visually for signs of microbial contamination. It should be stored in a colourless glass container and protected from light.

A clear, almost colourless, yellow, amber, or green slightly viscous liquid. A solution in sodium chloride 0.9% containing 1% protein has a pH of 6.7 to 7.3.

The **BP 2014** gives Albumin and Human Albumin as approved synonyms.

USP 36: (Albumin Human). A sterile, nonpyrogenic preparation of serum albumin obtained by fractionating material (blood, plasma, serum, or placentas) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It is made by a process that yields a product that is safe for intravenous use. It contains 4, 5, 20, or 25% of serum albumin and not less than 96% of the total protein is albumin. It may contain sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent; it contains no added antimicrobial agent. It contains 130 to 160 mmol of sodium per litre. It is a practically odourless, moderately viscous, clear, brownish fluid. It should be stored in airtight containers.

USNF 31: (rAlbumin Human). Recombinant Albumin Human (rHA) is produced by recombinant DNA expression in *Saccharomyces cerevisiae*. Structural equivalence (primary, secondary, and tertiary) between rHA and human serum albumin (HSA) has been demonstrated. It is presented as a sterile and nonpyrogenic aqueous liquid consisting of a 10% or 20% solution in Water for Injection. It contains no added antimicrobial agents, but it may contain appropriate stabilising agents. Clear, slightly viscous, and colourless to yellow amber in colour. Store in airtight glass containers at a temperature of 2 degrees to 8 degrees. Do not allow to freeze.

Uses and Administration

Albumin is the major protein involved in maintaining colloid osmotic pressure in the blood. It also binds several endogenous and exogenous substances including bilirubin, steroid hormones, and many, mainly acidic, drugs.

Albumin solutions are used for plasma volume replacement and to restore colloid osmotic pressure. They have been used in conditions such as burns, severe acute albumin loss, and acute hypovolaemic shock (p. 1279.3). They are also used as an exchange fluid in therapeutic plasmapheresis. Concentrated albumin solutions are used in neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn (p. 2377.2). They have also been suggested for short-term management of hypoproteinaemia in hepatic disease and in diuretic-resistant patients with nephrotic syndrome but are of little value in chronic hypoproteinaemias.

Albumin may be included in diagnostic preparations such as those labelled with technetium-99m (p. 2228.1) for use as radiopharmaceuticals in scanning of the heart, lung, liver, spleen, bone marrow, veins, and lymphatic system. Albumin labelled with iodine-125 (p. 2225.2) is used to measure blood and plasma volumes, blood circulation, and cardiac output. A suspension of albumin microspheres with perflutren (p. 1595.2) is available for enhancing cardiac ultrasound imaging.

Recombinant forms of human albumin have been developed as excipients for vaccines and other drug products, and for the treatment of hypoalbuminaemia and hypovolaemic shock.

Albumin solutions are usually available as 4.5% or 5% solutions, which are iso-osmotic with plasma, and as 20% or 25% solutions which are hyperosmotic with respect to plasma, and cause a movement of fluid from the extravascular to the intravascular compartment. These concentrated solutions may be used undiluted or may be diluted with a suitable solution, commonly sodium chloride 0.9% or glucose 5%. Adequate hydration should be maintained and electrolytes monitored in patients receiving hyperosmotic solutions of albumin.

The amount of albumin solution given will depend upon the clinical condition of the patient and the response to treatment. The following doses have been suggested:

- acute hypovolaemic shock: an initial dose of 25 g (for example, 500 mL of a 5% solution or 100 mL of a 25% solution)
- hypoproteinaemia: a maximum of 2 g/kg daily

The rate of intravenous infusion should be adjusted according to the indication and patient response, but in general, suggested rates of infusion are up to 5 mL/minute (5% solution) or 1 to 2 mL/minute (20% solution). In plasmapheresis the albumin infusion rate should be adjusted according to the rate of removal.

For the use of albumin in children, see below.

Albumin solutions should not be used for parenteral nutrition.

References.

1. Nicholson JP, *et al.* The role of albumin in critical illness. *Br J Anaesth* 2000; 85: 599–610.
2. Matejtschuk P, *et al.* Production of human albumin solution: a continually developing colloid. *Br J Anaesth* 2000; 85: 887–95.
3. Haynes GR, *et al.* Albumin administration—what is the evidence of clinical benefit? A systematic review of randomized controlled trials. *Eur J Anaesthesiol* 2003; 20: 771–93.
4. Mendez CM, *et al.* Albumin therapy in clinical practice. *Nutr Clin Pract* 2005; 20: 314–20.
5. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; 19: 157–67.
6. Kobayashi K. Summary of recombinant human serum albumin development. *Biologicals* 2006; 34: 55–9.

Administration in children. The amount and concentration of albumin solution given will depend upon the clinical condition of the patient and the response to treatment. When used in children the following doses, given by intravenous infusion, have been suggested:

- acute hypovolaemic shock: an initial dose of about 1 g/kg
- hypoproteinaemia: a maximum of 2 g/kg daily
- neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn: 1 g/kg before or during exchange transfusion (using a concentrated solution such as 25% albumin)

Adverse Effects and Precautions

Adverse reactions to albumin infusion occur rarely and include nausea and vomiting, increased salivation, flushing, urticaria, hypotension, tachycardia, and febrile reactions. These effects usually respond to slowing or stopping the infusion. Allergic reactions, including severe anaphylactic shock, are possible. Rapid increases in circulatory volume can cause vascular overload, hypertension, haemodilution, and pulmonary oedema. Solutions containing albumin 20 or 25% are hyperosmotic and draw fluid from the extravascular compartment.

Infusion of albumin solutions is contra-indicated in patients with severe anaemia or heart failure. They should be given with caution to patients with hypertension or low cardiac reserve. Dehydrated patients may require additional fluids. Injured or postoperative patients should be observed carefully when given albumin as the rise in blood pressure may result in bleeding from previously undetected sites.

Human albumin preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60 degrees, have reduced the risk of transmitting some viral infections.

Aluminium toxicity. Albumin solutions may contain appreciable amounts of aluminium. Marked increases in plasma-aluminium concentrations have been found in patients receiving large volumes by infusion and accumulation of aluminium may occur in patients with renal impairment.[1-3] In the UK albumin solutions with an aluminium content of less than 200 micrograms/litre are available for use in premature infants and patients undergoing dialysis.

1. Milliner DS, *et al.* Inadvertent aluminum administration during plasma exchange due to aluminum contamination of albumin-replacement solutions. *N Engl J Med* 1985; 312: 165–7.
2. Maher ER, *et al.* Accumulation of aluminium in chronic renal failure due to administration of albumin replacement solutions. *BMJ* 1986; 292: 306.
3. Maharaj D, *et al.* Aluminium bone disease in patients receiving plasma exchange with contaminated albumin. *BMJ* 1987; 295: 693–6.

Critically ill patients. Volume expansion with albumin (a colloid) has been widely used in critically ill patients, although its use had never been formally tested in large controlled studies. A systematic review based on available studies up to March 1998 (relatively small, old studies that recorded only a small number of deaths) suggested that albumin was of no benefit in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia, and that it might be linked to increased mortality.[1] The authors of the review stressed that these results should be treated with caution but nevertheless called for an urgent reconsideration of the use of albumin in critically ill patients.

The review was severely criticised[2] and while it was recognised that albumin had probably been overused in the past it was considered that more studies were required to define the effect of albumin on mortality.[3-5] Another review[6] found that the use of albumin did not significantly affect mortality; this meta-analysis had broader criteria and included studies that were considered to be relevant but that had been excluded by the other review.

In response to this debate, albumin 4% was compared with sodium chloride 0.9% for resuscitation in a study of 6997 hypovolaemic patients in intensive care (the SAFE study).[7] This large, randomised, double-blind study found equivalent rates of death from any cause during the 28-day study period. Survival-time during the 28 days, length of stay in the intensive care unit and in hospital, time on mechanical inhalation or renal replacement therapy, and development of organ failure were also similar. Although these two fluids seem clinically equivalent in a heterogeneous population of patients in intensive care, further study of selected groups, such as those with trauma or severe sepsis, is required.

An update to the original 1998 review included the results of SAFE. The authors maintained that patients with burns (a group excluded from the large study) or hypoproteinaemia might still be at risk of increased mortality, and although no longer suggesting a generally increased risk, concluded that there was no evidence that albumin reduced mortality in patients with hypovolaemia. Whether highly selected groups of critically ill patients might benefit is as yet unclear.[8]

Pharmacovigilance data reported to albumin suppliers over 3 years (1998 to 2000) have also been analysed.[9] During this period of heightened awareness about possible adverse effects of albumin, due to the publication of the 1998 review, a total of 1.62×10^7 doses of 40 g had been distributed. Serious adverse effects possibly or probably related to albumin were found to be rare, and no death was classified as probably related to albumin use.

On a broader level, debate continues about the relative merits and risks of such colloid solutions, compared with those of crystalloids such as glucose or sodium chloride solutions, in the management of hypovolaemia and shock (p. 1279.3).

1. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; 317: 235–40.
2. Various. Human albumin administration in critically ill patients. *BMJ* 1998; 317: 882–6. [Letters.]
3. Tomlin M. Albumin usage in the critically ill. *Pharm J* 1998; 261: 193.
4. McClelland B. Albumin: don't confuse us with the facts. *BMJ* 1998; 317: 829–30.
5. CSM/MCA. The safety of human albumin. *Current Problems* 1999; 25: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023246&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
6. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; 135: 149–64.
7. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350: 2247–56.
8. The Albumin Reviewers. Human albumin solution for resuscitation and volume expansion in critically ill patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 27/10/05).
9. Vincent J-L, *et al.* Safety of human albumin—serious adverse events reported worldwide in 1998–2000. *Br J Anaesth* 2003; 91: 625–30.

Dilution. If concentrated albumin solutions are to be diluted before use, a suitable solution such as sodium chloride 0.9% or glucose 5% must be used. Albumin 25% that was erroneously diluted with water to produce a hypo-osmolar albumin 5% solution has produced severe haemolysis and renal failure in patients undergoing plasmapheresis,[1,2] including one fatality.[3]

1. Steinmuller DR. A dangerous error in the dilution of 25 percent albumin. *N Engl J Med* 1998; 338: 1226.
2. Pierce LR, *et al.* Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. *Am J Health-Syst Pharm* 1998; 55: 1057,1062, 1070.
3. Anonymous. Hemolysis associated with 25% human albumin diluted with sterile water—United States, 1994–1998. *MMWR* 1999; 48: 157–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies albumin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Transmission of infections. There has been concern that albumin preparations may carry a potential risk of transmission of viral and subviral particles, notably Creutzfeldt-Jakob disease. In 1993, *Pasteur-Mérieux* (one of the largest producers of blood products) withdrew all products containing albumin derived from placental blood[1] due to uncertainty regarding the adequacy of screening procedures for placentas as a source. It was considered that the agent responsible for Creutzfeldt-Jakob disease might be contained in placentas from women who have been treated with growth hormone derived from cadaver pituitaries. More recently, the production of blood products (including albumin) using plasma from UK donors has been phased out due to the possible risk of transmission of new variant Creutzfeldt-Jakob disease.

1. Anonymous. Placental-derived albumin preparations withdrawn. *WHO Drug Inf* 1994; 8: 29–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Albuminar; Buminate; Flexbumin; Zenalb; *Austral.*: Albumex; *Austria*: Albunorm; *Belg.*: Albunorm; Alburex; Flexbumin; Octalbine; *Braz.*: Albuminar; Alburex; Beribumin; Blaubimax; Octalbin; Plasbumin; *Canad.*: Alburex; Albutein; Buminate; Plasbumin; *Chile*: Plasbumin†; *China*: Albuminar (亚玛); AlbuRx (安博灵); Albutein; Anpu Laishi (安普莱士); Buminate; Octapharma (奥达); Plasbumin (拜斯明); *Cz.*: Albunorm; Alburex; Flexbumin; *Denm.*: Albuminativ†; Flexbumin; Maasol; Nanocoll; Octalbin†; Venticoll; *Fin.*: Albuman; Albuminativ; Albunorm; Flexbumin; Octalbin; *Fr.*: Albunorm; Flexbumin; Octalbine†; Vialebex; *Ger.*: Albiomin; Albunorm; Alburex; Humanalbin; Plasbumin; *Gr.*: Albiomin; Albuman; Albuminar; Albuminativ; Alburex; Flexbumin; Hibumine; Nialbumin; Plasbumin; Zenalb; *Hong Kong*: Albumex; Albutein; Biseko; Buminate; Kamapharm†; NSA†; Plasbumin; *India*: Alba; Albudac; Albumed; Albumeon; Alburel; Albutein; Biseko; Humin; *Indon.*: Albapure; Albuminar; Alburaas; Albutein; Cealb; Farmin; Fimalbumin; Octalbin; Plasbumin; Robumin; Zenalb; *Irl.*: Albuminativ†; Albunorm; Flexbumin; *Israel*: Albiomin; Albuminativ; Egg Plus; Frosstimage Kit (MAA); Zenalb; *Ital.*: Albital; Alburex; Albutein; Nanocoll; Octalbin; Plasbumin; *Jpn*: Medway; *Malaysia*: Albutein; Buminate†; Zenalb; *Mex.*: Albunate; Octalbin; Vanderbumin†; *Neth.*: Albuman; Albunorm; Alburex; Cealb; Flexbumin; Octalbine; *Norw.*: Albuminativ†; Flexbumin; *NZ*: Albumex; Octalbin; *Philipp.*: Albumax; Albuminar; Alburel; Albutein; Kedrialb; Plasbumin; Plasbutein; Zenalb; *Pol.*: Biseko; *Port.*: Albiomin; Albuminativ†; Albunorm; Alburex; Flexbumin; *Rus.*: Plasbumin (Плазбумин); Zenalb (Зеналб); *S.Afr.*: Albusol; *Singapore*: Albutein; Buminate; NSA; Zenalb; *Spain*: Albiomin; Albunorm; Alburex; Albutein; Flexbumin; Octalbin†; Plasbumin; *Swed.*: Albuminativ; Albunorm; Flexbumin; *Switz.*: Flexbumin; *Thai.*: Albiomin; Alburaas; Albutein; Buminate; Flexbumin; Zenalb; *Turk.*: Alba; Albuman; Albuminar; Biotest Cealb; Plasbumin; Vialebex; Zenalb; *UK*: Albunorm; Alburex; Albutein; Flexbumin; Obruman; Zenalb; *USA*: Albumarc; Albuminar; AlbuRx; Albutein; Buminate†; Kedbumin; Plasbumin.

Multi-ingredient Preparations. *Denm.*: Pharmalgen Albumin; *Rus.*: Ferrohematogen (Феррогематоген); Hematogen C (Гематоген С); Hematogen C Vita (Гематоген С Вита); Hematogen Nova (Гематоген Новый); *Swed.*: Tisseel Duo Quick; *Ukr.*: Lactoprotein-C (Лактопротеин-С).

Pharmacopoeial Preparations
Ph. Eur.: Human Albumin Solution;
USP 36: Albumin Human.

Aminaphthone

Aminaftona; Aminaftone; Aminaphtone; Aminonaphthone. 2-Hydroxy-3-methylnaphtho-1,4-hydroquinone 2-(4-aminobenzoate); 3-Methylnaphthalene-1,2,4-triol, 2-(4-aminobenzoate).

$C_{18}H_{15}NO_4$=309.3
CAS — 14748-94-8.
UNII — 03JLX11PE9.

Profile

Aminaphthone is a haemostatic. Daily doses of 150 to 225 mg orally have been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Capilarema; *Ital.*: Capillarema; *Port.*: Capilarema.

Aminocaproic Acid *(BAN, USAN, rINN)*

Acide Aminocaproïque; Ácido aminocapróico; Ácido aminocaproico; Acidum Aminocaproicum; Aminocaproico, ácido; Aminocapronsäure; Aminokaproinhappo; Aminokaprono rūgštis; Aminokapronsav; Aminokapronsyra; CL-10304; CY-116; EACA; Epsilon Aminocaproic Acid; JD-177; Kwas ε-aminokapronowy; Kyselina aminokaproná; NSC-26154; Аминокапроновая Кислота.

6-Aminohexanoic acid.

$C_6H_{13}NO_2$=131.2
CAS — 60-32-2.
ATC — B02AA01.
ATC Vet — QB02AA01.
UNII — U6F3787206.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Aminocaproic Acid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 20% solution in water has a pH of 7.5 to 8.0.

USP 36: (Aminocaproic Acid). A fine, white, odourless or practically odourless, crystalline powder. Soluble 1 in 3 of water and 1 in 450 of methyl alcohol; slightly soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in acids and in alkalis. Its solutions are neutral to litmus. Store in airtight containers.

Uses and Administration

Aminocaproic acid is an antifibrinolytic used similarly to tranexamic acid (p. 1164.2) in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It has also been used in the prophylaxis of hereditary angioedema (p. 1132.1).

A plasma concentration of about 130 micrograms/mL is considered to be necessary for effective inhibition of fibrinolysis and the recommended dosage schedules are aimed at producing and maintaining this concentration for as long as is necessary. For the treatment of **haemorrhage**, aminocaproic acid may be given orally in an initial dose of 5 g, followed by 1 or 1.25 g every hour. Alternatively, similar doses may be given intravenously as a 2% solution; the initial dose (4 to 5 g) should be given over one hour followed by a continuous infusion of 1 g/hour. Up to 8 hours of treatment is often sufficient. Should treatment need to be extended, then the maximum dose over 24 hours should not normally exceed 24 g.

Aminocaproic acid may be given, usually with factor VIII or IX products, as prophylaxis or treatment in patients with **haemophilia** (p. 1126.3) who undergo dental extraction. Oral doses of 50 to 100 mg/kg (up to 6 g) may be given every 4 to 6 hours (maximum 24 g per 24 hours). Treatment may be started before the procedure, and is usually given for a total of 7 to 10 days.

Care is required when aminocaproic acid is used in patients with renal impairment and dosage should be reduced.

Hereditary angioedema. In the management of hereditary angioedema (p. 2485.2), antifibrinolytic drugs may be used as an alternative to androgens for the prophylaxis of attacks. The usual oral dose of aminocaproic acid in such patients is 1 g three or four times daily. It has also been used intravenously for acute attacks, and anecdotal reports suggest it may be modestly helpful, but there is no published evidence suggesting significant benefit.[1]

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; 114: 10–16.

Adverse Effects

Adverse effects associated with aminocaproic acid include dose-related gastrointestinal disturbances, dizziness, tinnitus, headache, nasal and conjunctival congestion, and rashes. Aminocaproic acid may cause muscle damage. This has usually occurred with high doses given for prolonged periods; renal failure may develop. Thrombotic complications have been reported, although they are usually a consequence of inappropriate use. If aminocaproic acid is given by rapid intravenous injection it can produce hypotension, bradycardia, and arrhythmias. There have been reports of a few patients suffering from convulsions, dry ejaculation, or cardiac and hepatic damage.

Effects on the blood. Very high doses of aminocaproic acid (36 g or more daily) have been given intravenously in the management of subarachnoid haemorrhage (see Stroke, p. 1269.2). One study[1] reported rebleeding and excessive intra-operative bleeding and suggested that this was due to an antiplatelet effect of the aminocaproic acid. However, a comment on this report[2] pointed out that any antiplatelet effect was independent of its antifibrinolytic action and that this effect could only aggravate rebleeding, if it occurs, rather than causing it. However, early surgical intervention is now used to manage subarachnoid haemorrhage, and in a series of 307 patients treated with high-dose short-term aminocaproic acid before early surgery it was found that, compared with older reports in the literature, there was a low rate of rebleeding without an apparent increase in adverse effects.[3]

1. Glick R, *et al.* High dose ε-aminocaproic acid prolongs the bleeding time and increases rebleeding and intraoperative hemorrhage in patients with subarachnoid hemorrhage. *Neurosurgery* 1981; 9: 398–401.
2. Kassell NF. Comment. *Neurosurgery* 1981; 9: 401.
3. Leipzig TJ, *et al.* Reducing the risk of rebleeding before early aneurysm surgery: a possible role for antifibrinolytic therapy. *J Neurosurg* 1997; 86: 220–5.

Effects on the kidneys. Adverse renal effects of aminocaproic acid are rare but have included renal arterial thrombosis, glomerular capillary thrombosis, and renal pelvic or ureteral obstruction caused by upper urinary tract thrombosis.[1] Cases of acute renal failure associated with myopathy are described under Effects on the Muscles, below.

1. Manjunath G, *et al.* Epsilon-aminocaproic acid and renal complications: case report and review of the literature. *Clin Nephrol* 2002; 58: 63–7.

Effects on the muscles. There have been cases of reversible myopathy,[1-4] associated with daily doses of aminocaproic acid ranging from 10 to 49 g and treatment durations of about 1 to 3 months. In some patients myoglobinuria or acute tubular necrosis also occurred. Suggested mechanisms for the reaction have included a direct dose-related effect on the muscle fibre[2] or a defect in aerobic energy provision induced by aminocaproic acid.[3]

1. Brown JA, *et al.* Myopathy induced by epsilon-aminocaproic acid. *J Neurosurg* 1982; 57: 130–4.
2. Vanneste JAL, van Wijngaarden GK. Epsilon-aminocaproic acid myopathy. *Eur Neurol* 1982; 21: 242–8.
3. Van Renterghem D, *et al.* Epsilon amino caproic acid myopathy: additional features. *Clin Neurol Neurosurg* 1984; 86: 153–7.
4. Seymour BD, Rubinger M. Rhabdomyolysis induced by epsilon-aminocaproic acid. *Ann Pharmacother* 1997; 31: 56–8.

Precautions

As for Tranexamic Acid, p. 1165.2.

The range of adverse effects that have been noted with aminocaproic acid indicates that caution is required in patients with renal or cardiac disorders. Should treatment be prolonged, it is advisable to monitor creatine phosphokinase values for signs of muscle damage.

Renal impairment. High anion gap metabolic acidosis developed in a 65-year-old woman with sepsis and acute renal failure who received aminocaproic acid for a haemorrhagic coagulopathy.[1] The acidosis improved temporarily after haemodialysis and resolved on withdrawal of aminocaproic acid and systemic alkalinisation. Although the dose of aminocaproic acid had been reduced because of renal impairment, it was suggested that more conservative dosing and close monitoring may be indicated in such patients. Hyperkalaemia has been attributed to the use of aminocaproic acid in a few patients with chronic renal failure.[2]

1. Budris WA, *et al.* High anion gap metabolic acidosis associated with aminocaproic acid. *Ann Pharmacother* 1999; 33: 308–11.
2. Nzerue CM, Falana B. Refractory hyperkalaemia associated with use of epsilon-aminocaproic acid during coronary bypass in a dialysis patient. *Nephrol Dial Transplant* 2002; 17: 1150–1.

Interactions

Retinoids. Aminocaproic acid should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p. 1727.1).

Pharmacokinetics

Aminocaproic acid is readily absorbed when given orally and peak plasma concentrations occur within 2 hours. It is widely distributed and is rapidly excreted in the urine, mainly unchanged, with a terminal elimination half-life of about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Caprocat; Ipsilon; *Braz.*: Ipsilon; *China*: Kai Nai Yin (凯乃银); *Fr.*: Hexalense†; *Hung.*: Acepramin; *India*: Hamostat; Hemocid; *Port.*: Epsicaprom; *Rus.*: Polycapran (Поликапран); *Spain*: Caproamin†; *Ukr.*: AKK (АКК); *USA*: Amicar; *Venez.*: Caproamin.

Multi-ingredient Preparations. *Braz.*: Eaca Balsamico; *Rus.*: Polygemostat (Полигемостат).

Pharmacopoeial Preparations
USP 36: Aminocaproic Acid Injection; Aminocaproic Acid Syrup; Aminocaproic Acid Tablets.

Aminomethylbenzoic Acid

Aminometilbenzoico, ácido; PAMBA; Аминометилбензойная Кислота.
4-Aminomethylbenzoic acid.
$C_8H_9NO_2$=151.2
CAS — 56-91-7.
ATC — B02AA03.
ATC Vet — QB02AA03.
UNII — 68WG9JKC7L

Profile

Aminomethylbenzoic acid is an antifibrinolytic with actions and uses similar to those of tranexamic acid (p. 1164.2). It is given orally in typical doses of 300 mg to 1 g daily, in 3 or 4 divided doses; it is also given by intramuscular injection, or intravenously by slow injection or infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An Ben (艾本); Ao Rui Ai (奥瑞艾); Fu Fen (弗芬); He Er Kang (赫尔康); Hong Yu Shu (虹雨舒); Ji Xiang Hong (吉祥红); Shuai Zhi (帅郅); Wei Ka (唯卡); *Cz.*: Pamba; *Ger.*: Pamba.

Multi-ingredient Preparations. *Ukr.*: Revalid (Ревалид).

Ancestim (USAN, rINN)

Ancestimum; r-metHuSCF; SCF; Stem Cell Factor; Анцестим.
N-L-Methionyl-1–165-haematopoietic cell growth factor KL (human clone V19.8:hSCF162), dimer.
CAS — 163545-26-4.
ATC — L03AA12.
ATC Vet — QL03AA12.
UNII — PYB4Q6JG41.

Uses and Administration

Ancestim is a recombinant human stem cell factor. It is used with filgrastim (p. 1151.3) to mobilise peripheral blood progenitor cells that are to be collected by apheresis harvest and used for autologous transplantation. The dose of ancestim is 20 micrograms/kg daily by subcutaneous injection; the injections of ancestim and filgrastim must be given at separate sites.

References.

1. Chin-Yee IH, *et al.* Optimising parameters for peripheral blood leukapheresis after r-metHuG-CSF (filgrastim) and r-metHuSCF (ancestim) in patients with multiple myeloma: a temporal analysis of CD34(+) absolute counts and subsets. *Bone Marrow Transplant* 2002; 30: 851–60.
2. Prosper F, *et al.* Mobilization of peripheral blood progenitor cells with a combination of cyclophosphamide, r-metHuSCF and filgrastim in patients with breast cancer previously treated with chemotherapy. *Leukemia* 2003; 17: 437–41.
3. To LB, *et al.* Successful mobilization of peripheral blood stem cells after addition of ancestim (stem cell factor) in patients who had failed a prior mobilization with filgrastim (granulocyte colony-stimulating factor) alone or with chemotherapy plus filgrastim. *Bone Marrow Transplant* 2003; 31: 371–8.
4. da Silva MG, *et al.* Ancestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior insufficient PBPC collection. *Bone Marrow Transplant* 2004; 34: 683–91.

Adverse Effects and Precautions

Injection site reactions commonly occur with the use of ancestim. Other skin reactions, including pruritus, rash, and urticaria, are less frequent. Systemic hypersensitivity reactions are also common and may be life-threatening. Premedication with antihistamines (both H_1- and H_2-antagonists) and an inhaled beta$_2$ agonist bronchodilator should be used, and the patient observed for at least an hour after ancestim is given. Tachycardia and respiratory symptoms including pharyngitis, dyspnoea, and cough, have also been reported.

Ancestim should not be given in the period from 24 hours before to 24 hours after a dose of cytotoxic chemotherapy or radiotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Stemgen; *Canad.*: Stemgen; *NZ*: Stemgen.

Antithrombin III (BAN, rINN)

Antithrombin III Human; Antithrombine III; Antithrombinum III; Antitrombiini III; Antitrombin III; Antitrombina III; Antitrombina III humana; Antytrombina III; AT-III; Cofactor I de la heparina; Heparin Cofactor; Heparin Cofactor I; Major Antithrombin; Антитромбин III.
CAS — 52014-67-2.
ATC — B01AB02.
ATC Vet — QB01AB02.
UNII — T0LTO7L82X.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Human Antithrombin III Concentrate; Antithrombinum III Humanum Densatum). A preparation of a glycoprotein fraction obtained from human plasma that inactivates thrombin in the presence of an excess of heparin. The plasma is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, distributed into sterile containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or in an atmosphere of inert gas. No antimicrobial preservative is added but a suitable stabiliser (such as albumin) is permitted. When reconstituted in the volume of solvent stated on the label, the resulting solution contains not less than 25 international units of antithrombin III per mL.

A white or almost white, hygroscopic, friable solid or powder. Store in airtight containers. Protect from light.

USP 36: (Antithrombin III Human). A glycoprotein, which is the major inhibitor of thrombin and other activated clotting factors, including factors IX, X, XI, and XII, and the cofactor through which heparin exerts its effect. It is obtained from human plasma of healthy donors who must, as far as can be ascertained, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. The method of manufacturing includes steps that have been shown to remove or inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, filled aseptically into its final, sterile containers, and immediately frozen. It is then freeze-dried, and the containers are closed under vacuum. No antimicrobial preservative is added at any stage of production. When reconstituted in the recommended volume of diluent, the pH is between 6.0 and 7.5, and the potency is not less than 25 USP units of antithrombin III per mL.

Store at a temperature of 2 degrees to 8 degrees, excursions permitted up to 25 degrees. Protect from light.

Antithrombin Alfa (USAN, rINN)

Antithrombine Alfa; Antithrombinum Alfa; Antitrombina alfa; Human Antithrombin III from the milk of transgenic goats (glycoform alfa); Recombinant Human Antithrombin; Антитромбин Альфа.

CAS — 84720-88-7.
UNII — AWV6I5L6H2.

Units

The potency of antithrombin III is expressed in international units and preparations may be assayed using the second International Standard for antithrombin concentrate (1997); each ampoule contains 4.7 international units of functional activity and 5.1 international units of antigenic activity.

One USP unit is described as the amount of antithrombin III that forms a complex with 1 unit of thrombin at 25 degrees in the presence of heparin at a pH of 8.4. Since assays of antithrombin III are carried out at 37 degrees, it is unclear whether USP units and international units are precisely equivalent, but in practice US preparations, like those elsewhere, appear to have their potency defined in international units.

The potency of antithrombin alfa is also expressed in international units.

Uses and Administration

Antithrombin III is a protein in plasma; it is the major endogenous inhibitor of thrombin and other activated clotting factors including factors IX, X, XI, and XII (p. 1124.3), and is the cofactor through which heparin (p. 1397.1) exerts its effect. Genetic and acquired deficiency of antithrombin III occurs and is associated with susceptibility to thromboembolic disorders.

Human plasma-derived antithrombin III is given intravenously to patients with antithrombin III deficiency in the treatment of thromboembolism and for prophylaxis associated with surgical and obstetric procedures. The aim of therapy is to restore plasma-antithrombin III concentrations to normal levels; the initial loading dose may be calculated to achieve 120% of normal, with maintenance doses aimed at concentrations between 80 and 120%. The dose, frequency, and duration of therapy are individualised for each patient taking into account the patient's pretreatment concentration and presence of active coagulation.

Antithrombin alfa is used similarly in the prophylaxis of venous thromboembolism in surgical and obstetric patients with congenital antithrombin III deficiency.

References.
1. Bucur SZ, *et al.* Uses of antithrombin III concentrate in congenital and acquired deficiency states. *Transfusion* 1998; **38**: 481–98.
2. Roemisch J, *et al.* Antithrombin: a new look at the actions of a serine protease inhibitor. *Blood Coag Fibrinol* 2002; **13**: 657–70.
3. Konkle BA, *et al.* Use of recombinant human antithrombin in patients with congenital antithrombin deficiency undergoing surgical procedures. *Transfusion* 2003; **43**: 390–4.

Septicaemia. Antithrombin III has been used in septicaemia (p. 203.2) in an attempt to manage the pro-coagulant state that occurs. Initial small studies reported a reduction in mortality[1] but a large controlled study[2] (KyberSept) found that treatment with antithrombin III had no effect on 28-day mortality. A further small observational study and meta-analysis also found no benefit from the use of antithrombin III in septicaemia.[3] These studies had used antithrombin III for less than 7 days, and a small study[4] in surgical patients with septicaemia found that 14 days of treatment with antithrombin III did improve measures of coagulation and fibrinolysis, the changes being most evident in the second week of therapy. However, the study was not large enough to test effects on mortality. Subsequent analysis of data from the KyberSept study appeared to show that 28-day mortality was in fact reduced in patients who had not been given heparin as well as antithrombin III;[5] combined use increased the risk of bleeding and apparently decreased the benefits of treatment with antithrombin III.

1. Eisele B, *et al.* Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 1998; **24**: 663–72.
2. Warren BL, *et al.* KyberSept Trial Study Group. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286**: 1869–78. Correction. *ibid.* 2002; **287**: 192.
3. Messori A, *et al.* Antithrombin III in patients admitted to intensive care units: a multicenter observational study. *Crit Care* 2002; **6**: 447–51.
4. Hoffmann JN, *et al.* Effect of long-term and high-dose antithrombin supplementation on coagulation and fibrinolysis in patients with severe sepsis. *Crit Care Med* 2004; **32**: 1851–9.
5. Hoffmann JN, *et al.* The KyberSept Investigators. Benefit/risk profile of high-dose antithrombin in patients with severe sepsis treated with and without concomitant heparin. *Thromb Haemost* 2006; **95**: 850–6.

Veno-occlusive disease. There is some evidence[1] from case reports and small studies that antithrombin III may have a beneficial effect on veno-occlusive disease associated with haematopoietic stem cell transplantation (p. 1937.1).

1. Ibrahim RB, *et al.* Anti-thrombin III in the management of hematopoietic stem-cell transplantation-associated toxicity. *Ann Pharmacother* 2004; **38**: 1053–9.

Adverse Effects and Precautions

Adverse effects of antithrombin III include flushing, headache, dizziness, chest tightness, nausea, a foul taste in the mouth, chills, and cramps. These can be controlled by slowing or stopping the infusion. Allergic reactions occur rarely. Injection site oozing and haematoma formation can occur, and haemorrhage (intra-abdominal, haemarthrosis, haematuria, and postprocedural) has been reported with the use of antithrombin alfa.

Human plasma-derived antithrombin III preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60 degrees, have reduced the risk of transmitting some viral infections. Antithrombin alfa is produced in the milk of transgenic goats, and should not be used in patients who are hypersensitive to goat proteins or goat milk components.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies antithrombin III as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Concomitant use of heparin and antithrombin III increases the risk of bleeding. Clinical effect and coagulation tests must be monitored and the dose of heparin adjusted as appropriate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Anbinex; Kybernin P; *Austral.*: Thrombotrol-VF; *Austria*: Atenativ; Kybernin P; Thrombhibin†; *Braz.*: Kybernin P; *Canad.*: Thrombate; *Cz.*: Anbinex; Atenativ; ATryn; Kybernin P; *Denm.*: Atenativ; ATryn†; *Fin.*: Atenativ; *Fr.*: Adotine; *Ger.*: Anbinex; AT III; Atenativ; Kybernin; *Gr.*: Atenativ; Atryn; Kybernin P; *Hung.*: Atenativ; Kybernin P; *Indon.*: Kybernin P; *Israel*: Anbinex; *Ital.*: Anbinex; Atenativ; Kybernin P; *Jpn*: Neuart; *Mex.*: Atend; Octati; *Neth.*: Atenativ; ATryn; *Norw.*: Atenativ; *NZ*: Thrombotrol-VF; *Pol.*: ATryn; *Port.*: Anbinex; Atenativ; ATryn; Kybernin P; *Singapore*: Anbinex; *Spain*: Anbinex; Atenativ; Kybernin P; *Swed.*: Atenativ; ATryn†; *Switz.*: Atenativ; Kybernin; *Turk.*: Anbin; Kybernin P; *UK*: ATryn; *USA*: ATryn; Thrombate III.

Pharmacopoeial Preparations
Ph. Eur.: Human Antithrombin III Concentrate;
USP 36: Antithrombin III Human.

Aprotinin *(BAN, USAN, rINN)*

Aprotinilni; Aprotinina; Aprotininas; Aprotinine; Aprotininum; Aprotynina; Bayer A-128; Riker 52G; RP-9921; Апротинин.

CAS — 9087-70-1.
ATC — B02AB01.
ATC Vet — QB02AB01.
UNII — 04XPW8C0FL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Aprotinin). A polypeptide consisting of 58 amino acids that inhibits the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It contains not less than 3 Ph. Eur. units/mg calculated with reference to the dried substance. An almost white, hygroscopic powder. Soluble in water and in isotonic solutions; practically insoluble in organic solvents. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Aprotinin Concentrated Solution). A solution of aprotinin containing not less than 15 Ph. Eur. units/mL. A clear colourless solution. Store in airtight containers. Protect from light.

USP 36: (Aprotinin). A polypeptide consisting of a chain of 58 amino acid residues, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It is obtained from bovine tissues and purified by a suitable process, and is stored as a bulk solution or lyophilised powder. Its potency is not less than 3 USP units/mg calculated with reference to the dried substance.

The lyophilised powder should be stored in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light. The bulk solution should be stored in airtight containers at a temperature not exceeding 25 degrees. Do not allow to freeze.

Incompatibility. Aprotinin is reported to be incompatible with corticosteroids, heparin, tetracyclines, and nutrient solutions containing amino acids or fat emulsions.

Units

The potency of aprotinin is expressed in terms of kallikrein (kallidinogenase) inactivator units (KIU) or of trypsin inactivation (Ph. Eur. units). One KIU is contained in 140 nanograms of aprotinin. One Ph. Eur. and one USP unit is equivalent to about 1800 KIU.

Potency has also been expressed in terms of plasmin inactivation (antiplasmin units).

Uses and Administration

Aprotinin is a haemostatic. It is an inhibitor of proteolytic enzymes including chymotrypsin, kallikrein (kallidinogenase), plasmin, and trypsin.

Aprotinin has been used to reduce blood loss and transfusion requirements in patients at increased risk of major blood loss during coronary artery bypass graft surgery with cardiopulmonary bypass. The marketing of aprotinin injection was suspended worldwide because of a possible increased risk of death associated with its use in cardiac surgery (see Haemorrhagic Disorders, below). However, in some countries, such as Canada, the resumption of marketing has been permitted, and it may be available in other countries, such as the USA, for investigational use using a special access protocol. It has also been used in the treatment of hyperfibrinolytic haemorrhage associated with raised plasma concentrations of plasmin. Aprotinin is applied topically as a component of fibrin glues (p. 1151.2).

It is recommended that because of the risk of hypersensitivity reactions an intravenous test dose of 10 000 KIU should be given to all patients at least 10 minutes before the therapeutic dose. All intravenous doses of aprotinin should be given through a central venous line.

In **coronary artery bypass graft surgery**, the test dose is followed by a loading dose given with the patient in a supine position, after induction of anaesthesia but before incision; 2 000 000 KIU is given intravenously over 20 to 30 minutes. The loading dose is followed by a continuous infusion of 500 000 KIU/hour until the end of the operation. An additional dose of 2 000 000 KIU is added to the prime volume of the extracorporeal circuit. The total amount of aprotinin used is usually no more than 7 000 000 KIU. A regimen using half the dose for loading, maintenance, and to prime the circuit, has been used in low-risk patients.

Haemorrhagic disorders. Aprotinin has been used in the treatment of life-threatening haemorrhage caused by raised plasma concentrations of plasmin. It has also been used in the treatment of severe bleeding arising from overdosage with thrombolytics (see Treatment of Adverse Effects under Streptokinase, p. 1506.3).

Aprotinin has been used to reduce blood loss in patients undergoing surgery, particularly cardiac surgery involving cardiopulmonary bypass. This bypass procedure is complicated by a postperfusion syndrome that includes impairment of haemostasis and pulmonary dysfunction. Contributing factors include ischaemia reperfusion, surgical trauma, endotoxaemia, and blood contact with the artificial surfaces of the bypass apparatus. This syndrome has been interpreted as a 'whole body inflammatory response', and the beneficial effect of aprotinin has been attributed to an attenuation of this response. As well as its inhibitory effect on fibrinolysis, aprotinin is thought to have effects on the complement system, cytokines, neutrophil activation, and platelet function.[1,2] Aprotinin has reduced blood loss and transfusion requirements in patients undergoing both primary and repeat cardiac surgery.[1,3-6] The usual dosage regimen (as given in Uses and Administration, above) and low-dosage regimens (50% of the usual dose) appear to be equally effective, but regimens that use aprotinin only as a pump prime dose appear to be less effective.[1,6]

The safety of aprotinin in cardiac surgery has been questioned, however, because of the results of two observational studies. One analysis[7] of patient outcome after the use of aminocaproic acid, aprotinin, tranexamic acid, or no treatment, found that although the three drugs had reduced blood loss to a similar extent, aprotinin was associated with an increased risk of cardiovascular and cerebrovascular events (myocardial infarction, heart failure, stroke, or encephalopathy) and renal failure. Observational follow-up also found that aprotinin, but not aminocaproic acid or tranexamic acid, was associated with an increased risk of death in the 5 years after surgery.[8] In another study[9] that compared data from patients who had received either aprotinin or tranexamic acid, there was an increased risk of renal dysfunction associated with aprotinin, particularly in patients with abnormal pre-operative renal function. In response to these studies, the FDA recommended[10] that patients receiving aprotinin should be carefully monitored, and that physicians should consider limiting its use to situations where the clinical benefit of reduced blood loss is essential and outweighs the potential risks.

The concerns raised by these studies and the FDA's recommendation prompted further analysis of data relating

to the effects of aprotinin. A meta-analysis[11] that included studies in different types of surgery, although the majority were in cardiac surgery, found no increased risk of death, cardiovascular events, or renal failure. However, because the reporting of renal function was lacking for many studies, and therefore a potential for bias, the authors were not confident that a modest increase in risk could be ruled out. Another meta-analysis[12] that was limited to studies in cardiac surgery also found no increased risk of death or cardiovascular events with aprotinin. There was also no increase in the risk of dialysis-dependent renal failure, but high-dose aprotinin did increase the risk of renal dysfunction, compared with placebo. Two large retrospective studies, which attempted to account for confounding variables, were also undertaken in cohorts of patients who had undergone coronary artery bypass graft surgery. One study found that, compared with aminocaproic acid, aprotinin increased the risk of in-hospital death.[13] The other found increased inpatient renal dysfunction, and death at 30 days and 1 year, in patients given aprotinin compared with aminocaproic acid or no antifibrinolytic therapy. Survival estimates also found an association between aprotinin use and reduced survival for up to 10 years after surgery.[14]

Preliminary data analysis from a randomised study (BART) also found an increased risk of death with aprotinin, compared with aminocaproic acid or tranexamic acid, and in November 2007, authorities such as the FDA[15] and EMEA[16] recommended that marketing of aprotinin injection be suspended. The BART study,[17] which was stopped early, included different types of high-risk cardiac surgery patients requiring cardiopulmonary bypass. Despite evidence of a modest reduction in the risk of massive bleeding, there was a strong and consistently negative mortality trend associated with aprotinin. The rate of death from any cause at 30 days was 6% in the aprotinin group, which equated to a relative risk of 1.53 (95% confidence interval, 1.06 to 2.22) compared with the combined results from patients given aminocaproic acid or tranexamic acid. In May 2008 the FDA confirmed that, in the USA, aprotinin injection would only be available for investigational use according to a special treatment protocol, for patients undergoing coronary artery bypass graft surgery requiring cardiopulmonary bypass.[18]

One of the meta-analyses[11] was updated in 2011 to include the results of subsequent studies including BART. This review[6] of randomised controlled studies concluded that although aprotinin was more effective than aminocaproic acid and tranexamic acid at minimising blood loss in cardiac surgery, it was associated with an increased risk of death. However, most of the data contributing to this risk was from the BART study. There was no significant increase in risk of myocardial infarction, stroke, other thrombotic events, or renal dysfunction. Around the same time, Canadian[19] and European[20] regulatory authorities also reviewed aprotinin information, concluding that the BART results were unreliable[20] and could not confirm an association between aprotinin and increased mortality.[19] Marketing suspension in Canada was lifted in 2011,[19] and a similar recommendation to resume marketing was made in Europe in 2012;[20] however, it was limited to patients at risk of major blood loss during isolated cardiopulmonary bypass surgery. Both regulatory authorities also advised on the importance of adequate anticoagulation with heparin during aprotinin treatment.

Aprotinin has been used to reduce transfusion requirements during liver transplantation, by its effect on intra-operative hyperfibrinolysis.[21,22] However, concerns about an increased risk of thromboembolism in these patients has been raised.[23] A systematic review[24] of 23 studies using antifibrinolytic drugs, 18 of which used aprotinin, found no evidence of an increased risk of thromboembolic complications in liver transplant patients, but noted that the studies were underpowered and that identification of subgroups of patients at risk may have been missed. Aprotinin has also been used to reduce transfusion requirements during orthopaedic surgery.[25]

1. Peters DC, Noble S. Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. *Drugs* 1999; 57 233–60.
2. Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg* 2001; 71: 745–54.
3. Bidstrup BP, *et al.* Aprotinin therapy in cardiac operations: a report on use in 41 cardiac centers in the United Kingdom. *Ann Thorac Surg* 1993; 55: 971–6.
4. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anesth Analg* 1997; 85: 1258–67.
5. Sedrakyan A, *et al.* Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004; 128: 442–8.
6. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 02/10/13).
7. Mangano DT, *et al.* The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354: 353–65.
8. Mangano DT, *et al.* Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007; 297: 471–9.
9. Karkouti K, *et al.* A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46: 327–38.
10. FDA. FDA Issues Public Health Advisory for Trasylol (issued 8th February, 2006). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108592.htm (accessed 13/08/10)
11. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).
12. Brown JR, *et al.* Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; 115: 2801–13.
13. Schneeweiss S, *et al.* Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med* 2008; 358: 771–83.
14. Shaw AD, *et al.* The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med* 2008; 358: 784–93.
15. FDA. FDA requests marketing suspension of Trasylol (issued 5th November, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109021.htm (accessed 13/08/10)
16. EMEA. European Medicines Agency recommends suspension of marketing authorisation of aprotinin-containing medicines for systemic use (issued 21st November, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015517.pdf (accessed 13/08/10)
17. Fergusson DA, *et al.* The BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; 358: 2319–31. Correction. *ibid.* 2010; 363: 1290.
18. FDA. Manufacturer removes remaining stocks of Trasylol; access limited to investigational use (issued 14th May, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116895.htm (accessed 13/08/10)
19. Bayer Healthcare. Notice to hospitals: Health Canada endorsed important safety information on Trasylol (aprotinin) (issued 19 September, 2011). Available at: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/14666a-eng.php (accessed 02/10/13)
20. EMA. European Medicines Agency recommends lifting suspension of aprotinin: review finds that benefits of all antifibrinolytic medicines outweigh risks in restricted range of indications (issued 17 February, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/02/WC500122914.pdf (accessed 02/10/13)
21. Porte RJ, *et al.* Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. *Lancet* 2000; 355: 1303–9.
22. Rentoul TM, *et al.* The effect of aprotinin on transfusion requirements in pediatric orthotopic liver transplantation. *Pediatr Transplant* 2003; 7: 142–8.
23. Lentschener C, *et al.* A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005; 100: 1248–55.
24. Molenaar IQ, *et al.* Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant* 2007; 7: 185–94.
25. Kokotska A, *et al.* Evidence-based review of the role of aprotinin in blood conservation during orthopaedic surgery. *J Bone Joint Surg Am* 2005; 87-A: 1129–36.

Pancreatitis. Aprotinin has been tried in the management of pancreatitis (p. 2580.2) because of the postulated role of proteolytic enzymes in this condition. However, results have been largely disappointing.

Adverse Effects and Precautions

Aprotinin is usually well tolerated. Local thrombophlebitis can occur. Adverse effects including bronchospasm, hypotension, cardiac arrhythmias, gastrointestinal disturbances, and rashes are considered to be hypersensitivity reactions; anaphylaxis, including fatalities, has occurred. The use of aprotinin is contra-indicated for 12 months after a previous exposure because of the increased risk of anaphylaxis during that time. A test dose is recommended for all patients and the use of prophylactic histamine antagonists may be considered; a hypersensitivity reaction to the therapeutic dose of aprotinin can still occur even after an uneventful test dose. There have been reports of renal dysfunction and reversible renal failure in patients given aprotinin during open-heart surgery with extracorporeal circulation; the risk may be increased in patients with pre-existing renal impairment or risk factors for altered renal function. For further details of an increased risk of cardiovascular and cerebrovascular events, renal failure, and death in patients undergoing surgery, and suspension of the marketing of aprotinin, see Haemorrhagic Disorders under Uses and Administration, p. 1133.3.

Disseminated intravascular coagulation. Fatal disseminated intravascular coagulation has been reported in a patient after the use of intraoperative autotransfusion and aprotinin during surgery.[1] Activation of the clotting system occurs during autotransfusion although this usually causes no systemic adverse effects. While there were other possible causes, it was suggested that aprotinin could have contributed to deposition of fibrin microthrombi in the microvasculature and prevented subsequent fibrinolysis.

1. Milne AA, *et al.* Disseminated intravascular coagulation after aortic aneurysm repair, intraoperative salvage autotransfusion, and aprotinin. *Lancet* 1994; 344: 470–1.

Effects on coagulation tests. Aprotinin prolongs both the activated partial thromboplastin time (APTT) and activated clotting time (ACT), depending on the ACT activation method used. However, aprotinin is not a heparin-sparing drug, and its effects on these tests may result in an overestimation in the degree of anticoagulation and subsequent underdosing of heparin. In patients undergoing cardiopulmonary bypass surgery, APTT should not be used alone to monitor coagulation parameters. ACT should also be used, taking into consideration the effect of aprotinin on the test in use; for example, a minimal celite-ACT of 750 seconds, or kaolin-ACT of 480 seconds, independent of the effects of haemodilution and hypothermia, have been recommended. Also, a fixed-dose heparin regimen or heparin-protamine titration method are suggested. Patients may require additional heparin during extended extracorporeal circulation, and protamine reversal of heparin should be based on a fixed ratio to the amount of heparin given, or be guided by protamine titration.

It should also be noted that aprotinin injection and heparin injection are pharmaceutically incompatible.

Effects on the respiratory system. Acute respiratory distress syndrome developed in a 24-year-old male 2 hours after the start of an intravenous infusion of aprotinin for bleeding after tonsillectomy.[1] Mechanical ventilation was required for 4 days.

1. Vucicevic Z, Suskovic T. Acute respiratory distress syndrome after aprotinin infusion. *Ann Pharmacother* 1997; 31: 429–32.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, can occur with the use of aprotinin both on primary and secondary exposure. In a study[1] of 248 re-exposures to aprotinin in 240 patients undergoing cardiac surgery, there were 7 cases of anaphylactic reactions ranging from mild to severe with a higher incidence of reactions occurring in those patients re-exposed within 6 months of the previous dose. A review[2] of 124 reported reactions in 122 patients also found that reactions ranged from mild to severe, and that about half were life-threatening and 11 were fatal. The risk of reaction was greatest with re-exposure to aprotinin as this had been the situation in 80% of the cases, although there were 19 cases associated with the first use of aprotinin. The average risk of anaphylaxis was estimated to be 2.8% in re-exposed patients. Most reactions occurred within 6 months of previous exposure, and the risk was greatest in the first 3 months. Various diagnostic tests have been tried in an attempt to predict hypersensitivity risk. Aprotinin-specific serum-IgG was reported to be detectable in about 50% of patients who had received only one aprotinin treatment, but other tests such as pre-operative skin testing were not found to be reliable.

Several measures have been suggested in order to reduce the risk of hypersensitivity reactions to aprotinin, including the use of an intravenous test dose in all patients, but it must be noted that these also have the potential to trigger a reaction.[1] For patients who have previously received aprotinin it has been recommended that re-exposure should be avoided for at least 6 months,[1,2] that aprotinin-specific antibody screening should be done,[2] and that prophylactic histamine H_1- and H_2-antagonists should be given to ameliorate severe anaphylactic reactions[1] although there are reports of reactions occurring despite antihistamine and corticosteroid prophylaxis.[2] It has also been suggested that in cardiac surgery, aprotinin should only be given when cardiopulmonary bypass is available to assist resuscitation.[1,2]

There have also been rare reports of hypersensitivity reactions on re-exposure to aprotinin used locally as a component of fibrin sealant.[3-5] In one fatal case[4] the previous exposure to fibrin sealant had been 5 years before.

1. Dietrich W, *et al.* Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997;113: 194–201.
2. Beierlein W, *et al.* Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; 79: 741–8.
3. Beierlein W, *et al.* An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000; 40: 302–5.
4. Oswald A-M, *et al.* Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; 99: 762–3.
5. Schlevink WI, *et al.* Anaphylactic reactions to fibrin sealant injection for spontaneous spinal CSF leaks. *Neurology* 2008; 70: 885–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aprotinin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Heparin. For comment on the use of aprotinin with heparin, see Effects on Coagulation Tests, above.

Neuromuscular blockers. For reports of apnoea when aprotinin was used with neuromuscular blockers, see p. 2032.2.

Retinoids. Aprotinin should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p. 1727.1).

Pharmacokinetics

Aprotinin, being a polypeptide, is inactivated in the gastrointestinal tract. After intravenous use, it is excreted in the urine as inactive degradation products. The terminal elimination half-life is about 5 to 10 hours.

Renal impairment. The terminal elimination half-life of aprotinin was reported as 13.3 and 14.9 hours, respectively, in two patients with chronic renal impairment given aprotinin by intravenous infusion over 30 minutes.[1] A study[2] of cardiac surgical patients undergoing cardiopulmonary bypass also found that aprotinin clearance was reduced in those with renal impairment. The elimination half-life was about 20 hours in patients with end stage renal disease compared with about 8 hours in those with creatinine clearance greater than 50 mL/min.

1. Müller FO, *et al.* Pharmacokinetics of aprotinin in two patients with chronic renal impairment. *Br J Clin Pharmacol* 1996; 41: 619–20.
2. O'Connor CJ, *et al.* The impact of renal dysfunction on aprotinin pharmacokinetics during cardiopulmonary bypass. *Anesth Analg* 1999; 89: 1101–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Quagu-Test; Rivilina; ***Belg.***: Trasylol†; ***Braz.***: Trasylol†; ***Canad.***: Trasylol; ***China***: Hetailin (赫泰林); Yi Mei Tai (意枚泰); ***Denm.***: Trasylol; ***India***: Aprogen; Apronin; Aprostat; Aprotec; Aprotin; Haemaprot; Haemoprot; Kallistat; ***Indon.***: Trasylol†; ***Israel***: Protosol; ***Philipp.***: Trasylol; ***Pol.***: Trasylol; ***Rus.***: Aprotex (Апротекс); Contrykal (Контрикал); Gordox (Гордокс); Ingitril (Ингитрил); Vero-Narcap (Веронаркап); ***S.Afr.***: Trasylol; ***Singapore***: Trasylol; ***Switz.***: Trasylol; ***Turk.***: Trasylol; ***Ukr.***: Contriven (Контривен); Contrycal (Контрикал); Gordox (Гордокс); Trasylol (Трасилол)†; ***Venez.***: Trasylol.

Multi-ingredient Preparations. ***Arg.***: Beriplast P; Lacrimax†; Maxus; Optilac; Tissucol; ***Austral.***: Tisseel Duo†; ***Austria***: Beriplast; Tisseel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Artiss; Tissucol Duo; Tissucol Kit; ***Braz.***: Beriplast P; ***Canad.***: Artiss; Tisseel; ***Chile***: Beriplast P†; ***Cz.***: Artiss; Tisseel; Tissucol; ***Denm.***: Artiss; Tisseel Duo Quick; ***Fin.***: Artiss; Tisseel Duo Quick; Tisseel; ***Fr.***: Artiss; Beriplast; Tissucol; ***Ger.***: Artiss; Beriplast; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Beriplast; Tisseel; ***Hong Kong***: Beriplast P; TachoComb; Tisseel; ***Hung.***: Beriplast P; Tissucol-Kit; ***Indon.***: Beriplast; ***Irl.***: Artiss; Tisseel; ***Israel***: Beriplast†; Tisseel†; ***Ital.***: Beriplast; Tissucol; ***Jpn***: Bolheal; ***Mex.***: Beriplast P; ***Neth.***: Artiss; Beriplast P; Tisseel; Tissucol Duo; Tissucol; ***Norw.***: Artiss; Tisseel; ***NZ***: Tisseel Duo; ***Pol.***: Beriplast; ***Port.***: Tissucol Duo†; ***Rus.***: TachoComb (ТахоКомб); Tissucol Kit (Тиссукол Кит); ***Singapore***: TachoComb; ***Spain***: Artiss; Beriplast P Combi; Tissucol Duo; ***Swed.***: Artiss; Tisseel Duo Quick; ***Switz.***: Artiss; Beriplast P; Tisseel; Tissucol Duo S†; Tissucol†; ***Thai.***: Tisseel; ***Turk.***: Beriplast P; Tisseel VH; ***UK***: Tisseel; ***USA***: Artiss; Tisseel.

Pharmacopoeial Preparations
USP 36: Aprotinin Injection.

Batroxobin *(rINN)*

Batroxobina; Batroxobine; Batroxobinum; Батроксобин.
CAS — 9039-61-6 (batroxobin); 9001-13-2 (haemocoagulase).
ATC — B02BX03.
ATC Vet — QB02BX03.
UNII — 47RYF40GA9.

Profile

Batroxobin is an enzyme obtained from the venom of the viper *Bothrops atrox*. It has also been obtained from *Bothrops moojeni* and a similar preparation is derived from *Bothrops jararaca*.

Batroxobin is reported to act on fibrinogen to produce a fibrin monomer that can be converted by thrombin to a fibrin clot. It is used both as a haemostatic and, in larger doses, to induce a hypofibrinogen state in the management of thromboembolic disorders. When used as a haemostatic it is usually given with a factor-X activator; such a combined preparation is known as haemocoagulase (hemocoagulase). Batroxobin has been given parenterally or by local application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bang Ting (邦亭); Reptilase (立正雪); Su Le Juan (速乐涓); Su Ling (苏灵); ***India***: Botroclot; Botropase; Colase; Reptilase.

Blood ⊗

Blod; Bloed; Blut; Sang; Sangre; Sangue; Sanguis; Vér; Veri; Кровь.
UNII — 43MX67MYM9.

Uses and Administration

Blood is a complex fluid with many functions including the maintenance of hydration of the tissues, maintenance of body temperature, and the transport within the body of gases, ions, nutrients, hormones, enzymes, antibodies, waste products of metabolism, and drugs.

The main components of blood are plasma, red blood cells (erythrocytes), white blood cells (leucocytes), and platelets (for further information on different blood cells and their formation, and average counts in adults, see Haematopoiesis, p. 1121.1). Serum is the fluid which remains once blood or plasma has clotted; it is, in effect, plasma with fibrinogen removed.

Whole blood is used as a source of red cell concentrates, clotting factors, platelets, plasma and plasma fractions, and immunoglobulins, each of which has specific indications for use. Because of the risks involved in transfusing whole blood and the need for economy in its use, the appropriate blood component should be used whenever possible.

Whole blood may be used where replacement of plasma proteins as well as red blood cells is needed, for example after acute blood loss during surgery or severe haemorrhage. It may also be used to supplement the circulation during cardiac bypass surgery.

The amount of whole blood transfused and the rate at which it is given depend upon the patient's age and general condition, upon the state of their circulatory system, and upon the therapeutic indication for transfusion.

The expression 'unit of blood' generally represents a volume of about 510 mL, including anticoagulant. For blood preparations a unit generally refers to the quantity of a blood component obtained from 1 unit of whole blood. Specific units of activity are used for some blood components.

The haemoglobin concentration of the blood of the average adult is raised by about 1 g per 100 mL by the transfusion of 1 unit of whole blood.

Reviews and guidelines for the use of blood and blood components.

1. Goodnough LT, *et al.* Transfusion medicine: blood transfusion. *N Engl J Med* 1999; 340: 438–47.
2. WHO. *The clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns.* Geneva: WHO, 2001. Also available as *The clinical use of blood handbook* at: http://whqlibdoc.who.int/publications/2001/9241545399.pdf (accessed 27/10/5)
3. Australian Red Cross Blood Service. *Transfusion medicine manual.* Available at: http://www.manual.transfusion.com.au/Home.aspx (accessed 29/08/08)
4. British Committee for Standards in Haematology Transfusion Task Force. Transfusion guidelines for neonates and older children. *Br J Haematol* 2004; 124: 433–53. Correction. *ibid.* 2007; 136: 514–16. Also available at: http://www.bcshguidelines.com/pdf/Neonates_124_4_2004.pdf (accessed 27/10/05)
5. British Committee for Standards in Haematology. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; 135: 634–41.
6. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/index.aspx?Publication=HTM (accessed 30/11/09)
7. American Red Cross. Practice guidelines for blood transfusion: a compilation from recent peer-reviewed literature, second edition (issued April 2007). Available at: http://www.redcross.org/www-files/Documents/WorkingWiththeRedCross/practiceguidelinesforbloodtrans.pdf (accessed 13/08/10)
8. Council of Europe. *Guide to the preparation, use and quality assurance of blood components.* 14th ed. Strasbourg: Council of Europe Publishing, 2008.
9. Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009.

Autologous blood transfusion. Reviews and guidelines have been published on autologous blood transfusion, a procedure where a patient acts as their own blood donor, the blood usually being collected shortly before elective surgery or salvaged during the surgical procedure.[1–6]

1. British Committee for Standards in Haematology Blood Transfusion Task Force. Guidelines for autologous transfusion II: perioperative haemodilution and cell salvage. *Br J Anaesth* 1997; 78: 768–71. Also available at: http://www.bcshguidelines.com/pdf/bja768.pdf (accessed 27/10/05)
2. Goodnough LT, *et al.* Transfusion medicine: blood conservation. *N Engl J Med* 1999; 340: 525–33.
3. Vanderlinde ES, *et al.* Autologous transfusion. *BMJ* 2002; 324: 772–5.
4. Carless P, *et al.* Autologous transfusion techniques: a systematic review of their efficacy. *Transfus Med* 2004; 14: 123–44.
5. British Committee for Standards in Haematology, Transfusion Task Force. Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion. *Transfus Med* 2007; 17: 354–65. Also available at: http://www.bcshguidelines.com/pdf/alt_allogeneic_blood_transfusion.pdf (accessed 09/06/08)
6. Thomas D, Hunt B. Alternatives to allogeneic blood transfusion. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 89–94.

Adverse Effects

The rapid transfusion of large volumes of whole blood may overload the circulation and cause pulmonary oedema. Transfusion of very large volumes of citrated blood can lead to hypocalcaemia, although this is not usually a problem unless there is hepatic impairment or hypothermia. Hyperkalaemia may occur but on its own is rarely clinically significant. Hypothermia may result from rapid transfusion of large volumes of cooled blood and may, combined with hypocalcaemia, hyperkalaemia, and resultant acidosis, lead to cardiotoxicity. Disseminated intravascular coagulation may also occur in patients receiving large-volume transfusions. Repeated transfusions of blood, as in thalassaemia, may lead to iron overload.

The transfusion of incompatible blood causes haemolysis, possibly with renal failure. Pyrexia, rigors, and urticaria may be due to antibodies towards blood components. Severe allergic reactions and anaphylaxis can occur. Delayed reactions may occur more than 24 hours after transfusion in patients in whom previous transfusion or pregnancy has induced sensitisation; these reactions are usually mild and manifest as fever, chills, fall in haemoglobin concentration, and haemoglobinuria.

Transmission of infections. The use of blood, blood components, or blood products has been associated with the transmission of viruses, most notably hepatitis B virus and HIV; other reports of transmission include CMV, hepatitis C and possibly other hepatitis viruses, HTLV-I and -II, and the prion causing variant Creutzfeldt-Jakob disease. Transmission of bacterial and parasitic diseases is also possible including syphilis, Chagas' disease, and malaria.

The main methods of minimising the risk of transmission of infection are by rigorous selection of blood donors and by microbiological screening tests. Contamination during collection and processing is minimised by using closed systems and by strict aseptic technique. Treatment of blood products with heat or chemicals can inactivate some organisms including some viruses, in particular HIV-1, but blood and blood components cannot be treated in either of these ways. Patients receiving multiple transfusions of pooled plasma products are at increased risk of contracting infections and can be offered immunological protection, for example hepatitis B vaccine.

Reviews.

1. Regan F, Taylor C. Blood transfusion medicine. *BMJ* 2002; 325: 143–7.
2. Goodnough LT. Risks of blood transfusion. *Crit Care Med* 2003; 31 (suppl): S678–S686.
3. Pomper GJ, *et al.* Risks of transfusion-transmitted infections: 2003. *Curr Opin Hematol* 2003; 10: 412–18.
4. Hardy J-F, *et al.* Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anesth* 2004; 51: 293–310.
5. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/index.aspx?Publication=HTM (accessed 30/11/09)
6. Kitchen AD, Barbara JAJ. Current information on the infectious risks of allogeneic blood transfusion. *Transfus Altern Transfus Med* 2008; 10: 102–11.
7. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; 113: 3406–17.
8. Contreras M, Navarrete C. Immunological complications of blood transfusion. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 61–8.
9. Barbara J, Contreras M. Infectious complications of blood transfusion: bacteria and parasites. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 69–73.
10. Barbara J, Contreras M. Infectious complications of blood transfusion: viruses. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 74–8.

Creutzfeldt-Jakob disease. While there is no proof that transmission of classical sporadic Creutzfeldt-Jakob disease by blood or blood products has occurred,[1–3] 4 cases have been reported of highly probable transmission of variant Creutzfeldt-Jakob disease (vCJD) by non-leucodepleted blood transfusion.[3–7] It is recognised that there is a need for further assessment of the potential risk of transmission of vCJD by such products.

Precautionary measures have been implemented in the UK to minimise transmission of vCJD by blood or tissues:[8]

- plasma is imported from outside the UK for fractionation to manufacture plasma derivatives
- leucocytes are removed from donated blood (leucodepletion) as it was thought that this would remove infectivity (however, *animal* studies have shown that this is not the case and that prion concentration in the blood is likely to be reduced by only about 40%[9])
- plasma is imported for clinical use in patients born after January 1996 (this date was chosen because it was considered that foods infected with bovine spongiform encephalopathy had been largely eliminated from the diet by this time[9]) and by July 2005 this had been extended to all patients under the age of 16
- donations of blood, platelets, and live bone are not accepted from donors who themselves have received blood components since 1 January 1980, or from any donors who have received intravenous immunoglobulin

prepared from UK plasma or who have undergone plasma exchange anywhere in the world

Concern at the risk of transmitting Creutzfeldt-Jakob disease by albumin prepared from placental blood has led to restriction on this source of albumin (see Transmission of Infections under Albumin, p. 1131.2).

1. Wilson K, *et al.* Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies. *BMJ* 2000; 321: 17–19.
2. Dorsey K, *et al.* Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. *Transfusion* 2009; 49: 977–84.
3. Hewitt P, *et al.* Variant Creutzfeldt-Jakob disease and its impact on the UK blood supply. In: Contreras M, ed. *ABC of transfusion.* 4th ed. Chichester: Wiley-Blackwell, 2009: 79–82.
4. Llewelyn CA, *et al.* Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004; 363: 417–21.
5. Peden AH, *et al.* Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; 364: 527–9.
6. Wroe SJ, *et al.* Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006; 368: 2061–7.
7. Turner ML, Ludlam CA. An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products. *Br J Haematol* 2009; 144: 14–23.
8. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/index.aspx?Publication=HTM (accessed 30/11/09)
9. Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products. *Br J Haematol* 2005; 132: 13–24.

Effects on leucocytes. A study of 50 patients in an intensive care unit found that 45 of them developed leucocytosis after transfusion of packed red blood cells.[1] The leucocytosis, which was accounted for by neutrophils, occurred immediately after transfusion and persisted for 12 hours. A further study[2] of 96 critically ill patients found that leucocytosis commonly occurred in those who were not septic and had received unfiltered packed red cells. Mean white cell counts were increased significantly 2 hours after infusion, remained elevated for about 12 hours, and returned to baseline by 24 hours. In 11 patients who required more than one transfusion, the use of filtered packed red cells was not associated with leucocytosis. Concentrations of interleukin-8 were found to be raised in unfiltered blood after 4 weeks of storage, and were higher in the transfused blood that caused leucocytosis. The authors suggested that cytokines produced by leucocytes in stored blood might be responsible for leucocytosis in recipients of unfiltered packed red cells.

1. Fenwick JC, *et al.* Blood transfusion as a cause of leucocytosis in critically ill patients. *Lancet* 1994; 344: 855–6.
2. Izbicki G, *et al.* Transfusion-related leukocytosis in critically ill patients. *Crit Care Med* 2004; 32: 439–42.

Effects on the lungs. A rare but life-threatening complication of transfusion of blood or other plasma-containing products is acute lung injury, often termed transfusion-related acute lung injury (TRALI). Symptoms develop during or within 6 hours of infusion and are those of acute respiratory distress syndrome[1-3] (p. 1599.3). Treatment is the same as for acute respiratory distress of any cause but oxygen exchange usually begins to improve between 24 and 48 hours; if the patient survives there appear to be no long-term sequelae.[1] The presence of HLA-specific antileucocyte antibodies in plasma from multiparous female donors appears to play a role in starting the reaction;[1,3] such antibodies have also been identified in some implicated male donors.[2] Another mechanism, the neutrophil priming hypothesis, proposes that TRALI results from 2 independent events. The first event causes the recipient's neutrophils to be primed and is related to the recipient's condition; in the second event the infused blood product activates the primed neutrophils in the lung, which causes endothelial damage.[2,3]

1. Wallis JP. Transfusion-related acute lung injury (TRALI)—underdiagnosed and under-reported. *Br J Anaesth* 2003; 90: 573–6.
2. Holness L, *et al.* Fatalities caused by TRALI. *Transfus Med Rev* 2004; 18: 184–8.
3. Kleinman S, *et al.* Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004; 44: 1774–89.

Graft-versus-host disease. Acute graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1937.1) has been reported in both immunocompromised and immunocompetent patients after blood transfusion.[1] Symptoms include fever, rash, abnormal liver function tests, diarrhoea, and pronounced leucopenia and pancytopenia. The reaction can be severe and fatal.

High-risk immunocompromised groups include bone marrow transplant recipients, patients with congenital immunodeficiencies, fetuses receiving intra-uterine transfusions, patients with Hodgkin's disease, and patients treated with purine analogue drugs such as fludarabine. Patients at less risk include those with acute leukaemia, non-Hodgkin's lymphoma, solid tumours treated with intensive chemotherapy or radiotherapy, premature infants and those undergoing exchange transfusion, and solid organ transplant recipients.

Immunocompetent patients who share an HLA haplotype with HLA-homozygous blood donors also appear to be at increased risk. Such cases have been reported particularly in Japan, where practices have included the use of transfusions from blood relatives. There is also a high incidence of shared haplotype in the population.

Infusion of products containing viable lymphocytes appears to be responsible. Treatment of graft-versus-host disease associated with transfusion is largely ineffective and patients considered to be at risk should be given products depleted of viable lymphocytes by irradiation. Blood products depleted of leucocytes by filtration still contain a small percentage of viable leucocytes, and this should not be used as the sole method to prevent graft-versus-host disease.

1. Schroeder ML. Transfusion-associated graft-versus-host disease. *Br J Haematol* 2002; 117: 275–87.

Malignant neoplasms. Perioperative allogeneic blood transfusion may be associated with an increase in the risk of recurrence, and decreased long-term survival, after resection of malignancy. This suggestion was based on retrospective observational studies, and was attributed to immunosuppressant effects of allogeneic blood. Randomised controlled studies have produced conflicting results, but a 1996 review[1] did not find a detrimental effect on the risk of cancer recurrence, and suggested that the findings of the observational studies probably resulted from the confounding effect of factors associated with the need for transfusion. A later meta-analysis[2] of 32 studies of perioperative transfusion in patients undergoing colorectal surgery concluded that the cancer recurrence rate was increased (odds ratio 1.68) in patients given transfusions. Risk factors associated with this increase were rectal disease, more advanced disease, and an increased number of transfused units. However, many of the included studies had small sample sizes, there was significant heterogeneity, and other possible surgery-related risk factors could not be evaluated, such that a causal association between the increased risk of cancer recurrence and transfusion could not be established. Other systematic reviews have come to different conclusions. A meta-analysis[3] of studies in patients undergoing resection of any type of solid tumour included only studies that used an active comparator (leucocyte-depleted or autologous blood). Only 8 studies met the inclusion criteria and the analysis provided no evidence of an increased risk of death or cancer recurrence in patients given allogeneic blood. The proposed detrimental immunosuppressive effect of perioperative allogeneic blood transfusion was studied in colorectal cancer patients given either allogeneic packed red cells (buffy coat removed) or leucocyte-depleted red cells.[4] Although the leucocyte count is reduced when the buffy coat is removed, more leucocytes are removed from leucocyte-depleted red cells, which should reduce any immunosuppressive effect. However, after 5 years there was no difference in survival or recurrence rates between the two groups. Survival was better for a third group of non-transfused patients, but this may be explained by a higher incidence of rectal cancer in the transfused groups, and the better clinical status of patients not requiring transfusion. A review[5] of individual studies and meta-analyses concluded that a causal relationship between allogeneic blood transfusion and solid cancer recurrence had not been proven. There was some evidence for transfusion-associated immunomodulation, but the mechanisms of effect and the specific constituents of allogeneic blood that mediate the effect remain unclear.

Epidemiological studies have reported an increase in the incidence of non-Hodgkin's lymphoma coinciding with the increase in the use of allogeneic blood transfusions since the 1950s. Proposed mechanisms have included transfusion-associated immunosuppression, transmission of oncogenic viruses, and blood donation by prelymphomatous donors.[6,7] Although some case-control studies have reported no association between blood transfusion and the development of non-Hodgkin's lymphoma,[8,9] others have reported a positive association, particularly for some subtypes of lymphoma.[10] Reviews[6,7] of these and other studies have found considerable disagreement between reports. This may result from biases in study design, confounding factors such as HIV infection, and lack of consensus on lymphoma classification.

1. Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. *Transfusion* 1996; 36: 175–86.
2. Amato AC, Pescatori M. Effect of perioperative blood transfusions on recurrence of colorectal cancer: meta-analysis stratified on risk factors. *Dis Colon Rectum* 1998; 41: 570–85.
3. McAlister FA, *et al.* Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies. *Br J Surg* 1998; 85: 171–8.
4. van de Watering LMG, *et al.* Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence. *Br J Surg* 2001; 88: 267–72.
5. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? *Blood* 2001; 97: 1180–95.
6. Vamvakas EC. Allogeneic blood transfusion as a risk factor for the subsequent development of non-Hodgkin's lymphoma. *Transfus Med Rev* 2000; 14: 258–68.
7. Chow EJ, Holly EA. Blood transfusions and non-Hodgkin's lymphoma. *Epidemiol Rev* 2002; 24: 269–79.
8. Maguire-Boston EK, *et al.* Blood transfusion and risk of non-Hodgkin's lymphoma. *Am J Epidemiol* 1999; 149: 1113–18.
9. Chow EJ, Holly EA. Blood transfusions as a risk factor for non-Hodgkin's lymphoma in the San Francisco Bay Area: a population-based study. *Am J Epidemiol* 2002; 155: 725–31.
10. Cerhan JR, *et al.* Blood transfusions and risk of non-Hodgkin's lymphoma subtypes and chronic lymphocytic leukemia. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 361–8.

Precautions

Whole blood should generally not be transfused unless the ABO and Rh groups of the patient's and the donor's blood have been verified and a compatibility check made between the patient's serum and the donor's red cells (see under Blood Groups, below).

The Rh group of the recipient should always be determined and ideally all patients should be transfused with blood of homologous Rh groups.

To reduce the possibility of cardiac arrest from cardiac hypothermia when large volumes are used or the blood is transfused rapidly, and to minimise postoperative shivering stored blood should be carefully warmed to about 37 degrees before transfusion.

Whole blood should not be given to patients with chronic anaemia who have a normal or elevated plasma volume.

Drugs should *not* be added to blood.

Transfusion of blood from donors who have recently been receiving drug treatment may be hazardous to the recipient.

Guidelines[1-4] for accepting blood from donors who have been receiving drugs have been published.

1. Ferner RE, *et al.* Drugs in donated blood. *Lancet* 1989; ii: 93–4.
2. Stichtenoth DO, *et al.* Blood donors on medication: are deferral periods necessary? *Eur J Clin Pharmacol* 2001; 57: 433–40.
3. UK Blood Transfusion Services. Whole blood and components donor selection guidelines: drug index (revised 23rd April, 2008). Available at: http://www.transfusionguidelines.org.uk/index.asp?Publication=D16-Section=4 (accessed 29/08/08)
4. American Red Cross. Eligibility criteria by topic. Available at: http://www.redcrossblood.org/donating-blood/eligibility-requirements/eligibility-criteria-topic (accessed 13/08/10)

Abuse. References to the infusion of whole blood or packed red blood cells to enhance athletic performance.[1,2]

1. Ekblom BT. Blood boosting and sport. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000; 14: 89–98.
2. Leigh-Smith S. Blood boosting. *Br J Sports Med* 2004; 38: 99–101.

Blood groups. The chief blood group systems are the ABO system and the Rhesus system.

In simple terms red blood cells carry on their surface genetically determined antigens. A person with antigen A, B, A plus B, or neither is classified as group A, B, AB, or O respectively. Such persons will have, in their serum, antibodies to B, A, neither, or both respectively—anti-B (β), anti-A (α), or anti-B plus anti-A (α + β). Giving blood containing red cells from a person of group A to a person with anti-A results in agglutination or possibly haemolysis. For the determination of the ABO group the agglutinogens of the red cells and the agglutinins of the serum are determined by testing against known standards.

In the Rhesus system many persons carry an antigen (Rh-positive) which stimulates antibody formation in Rh-negative persons; subsequent exposure to Rh-positive blood causes haemolysis.

Many variants of these and other systems, are recognised.

Calcium Alginate

Alginato cálcico; E404; Кальция Альгинат.

CAS — 9005-35-0.

ATC — B02BC08.

ATC Vet — QB02BC08.

UNII — 8P20S56HZI.

Profile

Calcium alginate is the calcium salt of alginic acid (p. 2167.2), a polyuronic acid composed of residues of D-mannuronic and L-guluronic acids. It may be obtained from seaweeds, mainly species of *Laminaria*. Calcium alginate is used as an absorbable haemostatic and for the promotion of wound healing (p. 1690.1); it is also used in the form of a mixed calcium-sodium salt of alginic acid as a fibre made into a dressing or packing material. Calcium ions in the calcium alginate fibres are exchanged for sodium ions in the blood and exudate to form a hydrophilic gel.

Alginic acid and its calcium and sodium salts are widely used in the food industry.

References.

1. Thomas S. Alginate dressings in surgery and wound management—part 1. *J Wound Care* 2000; 9: 56–60.

2. Thomas S. Alginate dressings in surgery and wound management: part 2. *J Wound Care* 2000; 9: 115–19.
3. Thomas S. Alginate dressings in surgery and wound management: part 3. *J Wound Care* 2000; 9: 163–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kaltostat; Nu-Derm Alginato; ***Austral.***: Algisite M; Melgisorb; Sorbsan; ***Belg.***: Algisite M; Algosteril; Askina Sorb; Kaltostat; Melgisorb; SeaSorb Soft; Sorbalgon; Suprasorb A; Tegaderm Alginate; Urgosorb; ***Canad.***: Kaltostat; Melgisorb; Restore CalciCare; Tegaderm Alginate; ***Fr.***: Algosteril; Coalgan; Stop Hemo; Suprasorb A; Tegaderm Alginate; ***Ger.***: Urgosorb; ***Gr.***: Stop Hemo; ***India***: Calkarlaa; ***Indon.***: Bioplacenton Tulle; ***Irl.***: Kaltostat†; Sorbsan†; ***Ital.***: Algosteril; Kaltostat; Melgisorb; Suprasorb A; ***S.Afr.***: Kaltostat; ***UK***: Algosteril; Comfeel SeaSorb; Kaltostat; Sorbsan; ***USA***: Calalgin.

Multi-ingredient Preparations. ***Arg.***: Comfeel Purilon; Comfeel SeaSorb; Fibracol Plus; Mylanta Reflux; Purilon†; SeaSorb†; ***Austral.***: Flaminal; ***Canad.***: Carboflex; ***Fr.***: Clip Hemo†; Melgisorb; Purilon; SeaSorb; Sorbalgon Plus; Urgosorb; ***Ger.***: Comfeel Plus; DracoAlgin; InfectoHoney Alginat†; Melgisorb Ag; Purilon; SeaSorb Soft; SeaSorb-Ag; Urgosorb Silver; ***Israel***: Kaltocarb; Kaltostat; ***Port.***: Kaltostat; ***Rus.***: Polygemostat (Полигемостат); ***UK***: Comfeel Plus; SeaSorb Soft.

Carbazochrome *(rINN)*

AC-17; Adrenochrome Monosemicarbazone; Carbazochromum; Carbazocromo; Monosemicarbazona de adrenocromo; Карбазохром.

3-Hydroxy-1-methyl-5,6-indolinedione semicarbazone.

$C_{10}H_{12}N_4O_3$=236.2

CAS — 69-81-8 (carbazochrome); 13051-01-9 (carbazochrome salicylate); 51460-26-5 (carbazochrome sodium sulfonate).

ATC — B02BX02.

ATC Vet — QB02BX02.

UNII — 81F061RQS4.

Pharmacopoeias. *Jpn* includes Carbazochrome Sodium Sulfonate ($C_{10}H_{11}N_4NaO_5S,3H_2O$ = 376.3).

Profile

Carbazochrome, an oxidation product of adrenaline, has been given as a haemostatic. Carbazochrome sodium sulfonate may be given orally in doses ranging from 30 to 150 mg daily, in at least 3 divided doses. Parenteral doses of 10 mg may be given subcutaneously or intramuscularly, and up to 100 mg may be given intravenously. It has also been given as the dihydrate and as the salicylate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Di Ka Ning (迪卡吟); Le Zhi Na (乐止纳); Luoye (洛叶); Na Neng (纳能); Su Bo Te (苏孛特); Tai Si Neng (太司能); Xue Yi Ting (雪益亭); ***Hong Kong***: Adona†; ***India***: Klog; Sigmachrome; Siochrome†; Styptocid; ***Indon.***: Adona; Adrome; Chromazol; Crome; ***Ital.***: Adona; ***Jpn***: Adona; ***Port.***: Adrenoxil†; ***Thai.***: Neo-Hesna†.

Multi-ingredient Preparations. ***India***: Cadisper C; CKP†; Siochrome; Styptocid; Styptocip; ***Ital.***: Fleboside; ***Jpn***: Behyd-RA; ***Mex.***: Hemosin-K; ***Spain***: Perfus Multivitaminico†.

Darbepoetin Alfa *(BAN, USAN, rINN)* ⊗

Darbepoetiinialfa; Darbepoetina alfa; Darbépoétine Alfa; Darbepoetinum Alfa; Darbepoyetina alfa; NESP; Novel Erythropoiesis Stimulating Protein; Дарбепоетин Альфа.

30-L-Asparagine-32-L-threonine-87-L-valine-88-L-asparagine-90-L-threonineerythropoietin (human).

CAS — 209810-58-2.

ATC — B03XA02.

ATC Vet — QB03XA02.

UNII — T5UQ94PT4P.

Uses and Administration

Darbepoetin alfa is an analogue of the endogenous protein hormone erythropoietin with similar properties to the epoetins (p. 1141.2). It is used in the management of anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p. 1123.1) and for anaemia caused by chemotherapy in patients with non-myeloid malignancies.

For **anaemia of chronic renal failure**, the aim of treatment is to use the lowest dose necessary to reduce the need for blood transfusion. A target haemoglobin range of 10 to 12 g per 100 mL has been used, but US licensed product information now recommends that darbepoetin alfa therapy may be considered when the haemoglobin concentration is less than 10 g per 100 mL, and to reduce the dose or stop therapy if the concentration exceeds 10 g per 100 mL in patients not on dialysis or when it approaches or exceeds 11 g per 100 mL in patients on dialysis (see also Haematocrit and Haemoglobin, under Precautions of Epoetins, p. 1144.3). The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 1 g per 100 mL in any 2-week period, or 2 g per 100 mL per month, is suggested.

Darbepoetin alfa is given by subcutaneous or intravenous injection. In patients on haemodialysis, the intravenous route is recommended to reduce the risk of developing neutralising antibodies and pure red cell aplasia (see Effects on the Blood under Epoetins, p. 1143.3); the subcutaneous route is preferable in those not receiving haemodialysis to avoid puncture of the peripheral veins. Various dosage regimens can be found in licensed product information. Initial doses for patients on haemodialysis include:

- 450 nanograms/kg once weekly
- 750 nanograms/kg once every 2 weeks

For patients not on dialysis, recommendations include:

- 450 nanograms/kg once weekly
- 450 nanograms/kg once every 4 weeks
- 750 nanograms/kg once every 2 weeks
- 1.5 micrograms/kg once every month

The dose may be increased at intervals of not less than 4 weeks, according to response, until the target haemoglobin concentration is achieved. In general, adjustments are made by increasing or decreasing the dose by about 25%. For maintenance therapy patients may be converted from weekly doses to once every 2 weeks, and should receive a dose that is equal to twice the dose that had been given once weekly. Those given an initial dose once every 2 weeks may be converted to a maintenance dose given once a month; this is equal to twice the dose that had been given once every 2 weeks.

Darbepoetin alfa may be used for treating symptomatic chemotherapy-associated anaemia in patients with **non-myeloid malignant disease**. However, US licensed product information cautions that it is not indicated when the anticipated outcome is cure, as the impact of darbepoetin alfa therapy on progression-free and overall survival has not been adequately studied. See also Anaemias (under Epoetins, p. 1142.3) for FDA restrictions on the prescribing of darbepoetin alfa for patients with cancer, and advice from the MHRA on when blood transfusion may be the preferred therapy.

Darbepoetin alfa is given subcutaneously in an initial dose of 500 micrograms (6.75 micrograms/kg) once every 3 weeks; if the response is inadequate after 9 weeks, further therapy with darbepoetin alfa may not be effective. Alternatively, it may be given in an initial dose of 2.25 micrograms/kg once weekly. If the response is inadequate after 6 weeks, the dose may be increased to 4.5 micrograms/kg once weekly. Darbepoetin alfa should be stopped after the course of chemotherapy has finished, but UK licensed product information states that it may be continued for up to 4 weeks. The rate of rise in haemoglobin should be gradual; a rate not exceeding 2 g per 100 mL per month, and a target haemoglobin of not more than 12 g per 100 mL, are suggested. Once the desired haemoglobin target has been reached, the dose should be reduced by 25 to 50% to maintain that level.

Darbepoetin alfa is under investigation in the management of patients with anaemia and heart failure.

Reviews.
1. Ibbotson T, Goa KL. Darbepoetin alfa. *Drugs* 2001; 61: 2097–2104.
2. The NESP Usage Guidelines Group. Practical guidelines for the use of NESP in treating renal anaemia. *Nephrol Dial Transplant* 2001; 16 (suppl 3): 22–8.
3. Overbay DK, Manley HJ. Darbepoetin-α : a review of the literature. *Pharmacotherapy* 2002; 22: 889–97.
4. Joy MS. Darbepoetin alfa: a novel erythropoiesis-stimulating protein. *Ann Pharmacother* 2002; 36: 1183–92.
5. Cvetkovic RS, Goa KL. Darbepoetin alfa in patients with chemotherapy-related anaemia. *Drugs* 2003; 63: 1067–74.
6. Siddiqui MAA, Keating GM. Darbepoetin alfa: a review of its use in the treatment of anaemia in patients with cancer receiving chemotherapy. *Drugs* 2006; 66: 997–1012.

Administration in children. Darbepoetin alfa therapy may be used in children for the treatment of anaemia associated with chronic renal failure. It may be started in children aged 11 years and older in doses similar to those used in adults (see above).

Adverse Effects and Precautions

As for Epoetins, p. 1143.3 and p. 1144.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies darbepoetin alfa as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

On subcutaneous injection the bioavailability of darbepoetin alfa is about 37% and absorption is slow. A terminal half-life of about 21 hours has been found after intravenous use in patients with chronic renal failure who were receiving dialysis. After subcutaneous use a half-life of about 46 hours has been found in patients receiving dialysis, while it was about 70 hours in those with chronic renal failure but not receiving dialysis, and about 74 hours in patients with cancer.

References.
1. Heatherington AC, *et al.* Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) in cancer patients: preliminary report. *Br J Cancer* 2001; 84 (suppl): 11–16.
2. Allon M, *et al.* Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. *Clin Pharmacol Ther* 2002; 72: 546–55.
3. Lerner G, *et al.* Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. *Pediatr Nephrol* 2002; 17: 933–7.
4. Heatherington AC, *et al.* Pharmacokinetics of darbepoetin alfa after intravenous or subcutaneous administration in patients with non-myeloid malignancies undergoing chemotherapy. *Clin Pharmacokinet* 2006; 45: 199–211.
5. Padhi D, *et al.* An extended terminal half-life for darbepoetin alfa: results from a single-dose pharmacokinetic study in patients with chronic kidney disease not receiving dialysis. *Clin Pharmacokinet* 2006; 45: 503–10.
6. Takama H, *et al.* Population pharmacokinetics of darbepoetin alfa in haemodialysis and peritoneal dialysis patients after intravenous administration. *Br J Clin Pharmacol* 2007; 63: 300–309.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aranesp; ***Austria***: Aranesp; ***Belg.***: Aranesp; ***Canad.***: Aranesp; ***Cz.***: Aranesp; Nespo†; ***Denm.***: Aranesp; ***Fin.***: Aranesp; ***Fr.***: Aranesp; ***Ger.***: Aranesp; ***Gr.***: Aranesp; ***Hong Kong***: Aranesp; ***Hung.***: Aranesp; ***Irl.***: Aranesp; ***Israel***: Aranesp; ***Ital.***: Aranesp; Nespo†; ***Neth.***: Aranesp; ***Norw.***: Aranesp; ***NZ***: Aranesp; ***Pol.***: Aranesp; ***Port.***: Aranesp; ***Rus.***: Aranesp (Аранесп); ***Singapore***: Aranesp†; Nesp; ***Spain***: Aranesp; ***Swed.***: Aranesp; ***Switz.***: Aranesp; ***Thai.***: Nesp; ***Turk.***: Aranesp; ***UK***: Aranesp; ***USA***: Aranesp.

Dextran 1 *(BAN, rINN)* ⊗

Dekstraani 1; Dekstranas 1; Dextrán 1; Dextrano 1; Dextranum 1; Декстран 1.

CAS — 9004-54-0 (dextran).

ATC — B05AA05.

ATC Vet — QB05AA05.

UNII — I8LHQOD645.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Dextran 1 for Injection). A low-molecular-weight fraction of dextran, consisting of a mixture of isomalto-oligosaccharides. It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 1000.

A white or almost white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol.

USP 36: (Dextran 1). A low-molecular-weight fraction of dextran, consisting of a mixture of isomalto-oligosaccharides. It is obtained by controlled hydrolysis and fractionation of dextrans produced by fermentation of certain strains of *Leuconostoc mesenteroides*, in the presence of sucrose. It is a glucose polymer in which the linkages between glucose units are almost exclusively α-1,6. Its weight average molecular weight is about 1000.

A white to off-white, hygroscopic powder. Very soluble in water; sparingly soluble in alcohol. pH of a 15% solution in water is between 4.5 and 7.0. Store at a temperature between 4 degrees and 30 degrees.

Profile

Dextran 1 is used to prevent severe anaphylactic reactions to infusions of dextran. It is reported to occupy the binding sites of dextran-reactive antibodies and so prevent the formation of large immune complexes with higher molecular weight dextrans.

Dextran 1 is given in usual doses of 20 mL of a solution containing 150 mg/mL by intravenous injection about 1 to 2 minutes before the infusion of the higher molecular weight dextran; the interval should not exceed 15 minutes. The dose of dextran 1 should be repeated if further infusions of dextran are required more than 48 hours after the initial dose. For doses used in children, see below.

Administration in children. A suggested intravenous dose of dextran 1 for children is 0.3 mL/kg of a solution containing 150 mg/mL.

Use. Two large multicentre studies (involving about 29 200 and 34 950 patients) have suggested that dextran 1

prevented anaphylactic reactions by hapten inhibition in a dose-dependent way.[1,2] It did not reduce the incidence of mild reactions, which are not generally mediated by antibodies. Another large study[3] comparing the effects of giving dextran 1 either 2 minutes before injection of dextran 40 or 70 or mixed with the injection, was stopped after the occurrence of 2 severe reactions in the admixture group. A comparison[4] of severe anaphylactic reactions to dextran infusion during the period 1983 to 1992 (when prophylaxis with dextran 1 was used) with reactions reported during the period 1975 to 1979 (no prophylaxis) found that the use of dextran 1 was associated with a 35-fold reduction in severe anaphylactic reactions to dextran infusion.

There were 21, 20, and 2 adverse reactions to dextran 1 in the first 3 studies respectively, including nausea, skin reactions, bradycardia, and hypotension. Apart from one patient, reactions to dextran 1 were mild and were considered to be of minor clinical importance. In the fourth study, adverse effects to dextran 1 were reported in about one case per 100 000 doses.

1. Ljungström K-G, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition I: a Scandinavian multicenter study on the effects of 10 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983; 149: 341–8.
2. Renck H, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition II: Scandinavian multicenter study on the effects of 20 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983; 149: 355–60.
3. Renck H, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition II: a comparison of the effects of 20 mL dextran 1, 15% administered either admixed to or before dextran 70 or dextran 40. *Acta Chir Scand* 1983; 149: 349–53.
4. Ljungström K-G. Safety of dextran in relation to other colloids - ten years experience with hapten inhibition. *Infusionsther Transfusionsmed* 1993; 20: 206–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Promit; *Denm.*: Promiten; *Hung.*: Promiten; *Norw.*: Promiten; *S.Afr.*: Promit†; *Swed.*: Promiten; *USA*: Promit†.

Dextran 40 *(BAN, USAN, rINN)* ⊗

Dekstraani 40; Dekstran 40; Dekstranas 40; Dextrán 40; Dextrano 40; Dextranum 40; LMD; LMWD; Low-molecular-weight Dextran; LVD; Декстран 40.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — K3R6ZDH4DU.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

Eur. (see p. vii) and *Jpn* describe Dextran 40 for Injection.

Ph. Eur. 8: (Dextran 40 for Injection). A mixture of polysaccharides, mainly of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 40 000.

A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

USP 36: (Dextran 40). It is derived by controlled hydrolysis and fractionation of polysaccharides elaborated by the fermentative action of certain strains of *Leuconostoc mesenteroides* on a sucrose substrate. It is a glucose polymer in which the linkages between glucose units are almost entirely of the α-1:6 type. Its weight average molecular weight is in the 35 000 to 45 000 range. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 40 preparations.

Uses and Administration

Dextran 40 is a plasma volume expander used in the management of hypovolaemic shock (p. 1279.3). As a 10% solution, dextran 40 exerts a slightly higher colloidal osmotic pressure than plasma proteins and thus produces a greater expansion of plasma volume than dextrans of a higher molecular weight, although the expansion may have a shorter duration because of more rapid renal excretion. Dextran 40 also reduces blood viscosity and inhibits sludging or aggregation of red blood cells. It is used in the prophylaxis and treatment of postoperative thromboembolic disorders, in conditions where improved circulatory flow is required, and as a priming solution during extracorporeal circulation.

Dextran 40 is given by intravenous infusion as a 10% solution in sodium chloride 0.9% or glucose 5%. Doses depend on the clinical condition of the patient.

In shock, a maximum of 20 mL/kg during the first 24 hours has been recommended; the first 10 mL/kg may be given by rapid intravenous infusion. Doses of up to 10 mL/kg may be given daily thereafter for up to 5 days. Dehydration should preferably be corrected before dextran 40 is given.

In the treatment of **thromboembolic disorders** a suggested regimen is 500 to 1000 mL over 4 to 6 hours on the first day, then 500 mL over 4 to 6 hours on the next and subsequent alternate days for not more than 10 days.

For prophylaxis of postoperative thromboembolic disorders, 500 mL over 4 to 6 hours may be given during or at the end of surgery and the dose repeated on the next day; treatment may be continued in high risk patients on alternate days for up to 10 days.

A dose of 10 to 20 mL/kg has been added to extracorporeal perfusion fluids.

Dextran 40 is also an ingredient of artificial tears.

Post-dural puncture headache. Dextran 40 has been used in the treatment of post-dural puncture headache (p. 1983.1) when other measures, including epidural autologous blood patch, have been ineffective. Reports[1-3] have described dextran 40 given in an epidural bolus dose of 20 mL. Sometimes this has been followed by a continuous epidural infusion of 3 to 4 mL/hour, and in these cases headache was relieved within 20 hours of starting the infusion.[1,2]

1. Aldrete JA. Persistent post-dural-puncture headache treated with epidural infusion of dextran. *Headache* 1994; 34: 265–7.
2. Reynvoet MEJ, *et al.* Epidural dextran 40 patch for postdural puncture headache. *Anaesthesia* 1997; 52: 886–8.
3. Souron V, Hamza J. Treatment of postdural puncture headaches with colloid solutions: an alternative to epidural blood patch. *Anesth Analg* 1999; 89: 1333–4.

Thromboembolic disorders. Dextran 40 is only one of a variety of drugs that have been used for the prophylaxis of venous thromboembolism (p. 1274.1) resulting from surgical operations such as hip replacement surgery. Dextran 40 may be used to prevent thromboembolic complications in some types of vascular surgery including carotid endarterectomy.[1]

1. Abir F, *et al.* Efficacy of dextran solutions in vascular surgery. *Vasc Endovascular Surg* 2004; 38: 483–91.

Adverse Effects, Treatment, and Precautions

As for Dextran 70, p. 1139.1.

Rapid renal excretion of dextran 40 in patients with reduced urine flow can result in high urinary concentrations which increase urinary viscosity and may cause oliguria or acute renal failure. Therefore, infusions of dextran 40 are contra-indicated in renal disease with oliguria; should anuria or oliguria occur during treatment dextran 40 should be withdrawn. Dehydration should preferably be corrected before giving dextran 40. Dextran 40 can cause capillary oozing of wound surfaces.

Effects on the kidneys. Acute renal failure has been associated with dextran 40[1-4] and less frequently with dextran 70.[1] The mechanism of the effect is unclear but suggestions include an increase in plasma oncotic pressure that decreases filtration pressure in the glomerulus and hence decreases glomerular filtration rate,[2] obstruction within the tubules,[2,4] or a direct toxic effect on renal cells.[4] Plasmapheresis has been used successfully to remove dextran from the circulation.[2-4]

1. Peers TG. Low molecular weight dextran: a continuing cause of acute renal failure. *BMJ* 1976; 2: 1300.
2. Tsang RKY, *et al.* Acute renal failure in a healthy young adult after dextran 40 infusion for external-ear reattachment surgery. *Br J Plast Surg* 2000; 53: 701–3.
3. Kato A, *et al.* Complication of oliguric acute renal failure in patients treated with low-molecular weight dextran. *Ren Fail* 2001; 23: 679–84.
4. Vos SCB, *et al.* Acute renal failure during dextran-40 antithrombotic prophylaxis: report of two microsurgical cases. *Ann Plast Surg* 2002; 48: 193–6.

Hypersensitivity. For reports of anaphylactic reactions associated with use of dextran 40, see Dextran 70, p. 1139.1, and Dextran 1, p. 1137.3.

Pharmacokinetics

After intravenous infusion dextran 40 is slowly metabolised to glucose. About 70% of a dose is excreted unchanged in the urine within 24 hours. A small amount is excreted into the gastrointestinal tract and eliminated in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Fu Ta Le (福他乐); Shen Shui Qing (肾水清); Xin Run Luo (欣润络); *Denm.*: Rheomacrodex; *Gr.*: Deltadex; Gentran; Neodextril; *Hung.*: Rheomacrodex; *India*: Microspan-40; *Indon.*: Otsutran; *Ital.*: Eudextran; Plander R; *Jpn*: Saviosol; *Mex.*: Rheomacrodex†; *Norw.*: Rheomacrodex; *Philipp.*: LM Dextran; *Port.*: Bas-Dextrano†; Neodextril 40; *Rus.*: Haemostabil (Гемостабил) Rheomacrodex (Реомакродекс)†; Rheopolydex (Реополидекс) Rheopolyglukin (Реополиглюкин); *S.Afr.*: Rheomacrodex; *Singapore*: Onkovertin; *Spain*: Rheomacrodex; *Swed.*: Perfadex Rheomacrodex; *Thai.*: Onkovertin†; *Turk.*: Rheomacrodex *UK*: Gentran 40; *USA*: Gentran 40; Rheomacrodex.

Multi-ingredient Preparations. *Rus.*: Rheogluman (Реоглюман).

Pharmacopoeial Preparations
BP 2014: Dextran 40 Infusion;
USP 36: Dextran 40 in Dextrose Injection; Dextran 40 in Sodium Chloride Injection.

Dextran 60 *(BAN, rINN)* ⊗

Dekstraani 60; Dekstranas 60; Dextrán 60; Dextrano 60; Dextranum 60; Декстран 60.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — ZNJ8R24I7Z.

Pharmacopoeias. *Eur.* (see p. vii) describes Dextran 60 for Injection.

Ph. Eur. 8: (Dextran 60 for Injection). A mixture of polysaccharides, mainly of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 60 000.

A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 60 preparations.

Profile

Dextran 60 is a plasma volume expander with actions and uses similar to those of dextran 70 (below). It is given by intravenous infusion as a 3 or 6% solution in sodium chloride 0.9% or a mixture of electrolytes.

Dextran 60 is also used topically for dry eyes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Macrodex; *Norw.*: Plasmodex; *Swed.*: Plasmodex.

Dextran 70 *(BAN, USAN, rINN)* ⊗

Dekstraani 70; Dekstran 70; Dekstranas 70; Dextrán 70; Dextrano 70; Dextranum 70; Polyglucin (dextran); Декстран 70.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — 7SA290YK68.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

Eur. (see p. vii) describes Dextran 70 for Injection.

Ph. Eur. 8: (Dextran 70 for Injection). A mixture of polysaccharides, mainly of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 70 000.

A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

USP 36: (Dextran 70). It is derived by controlled hydrolysis and fractionation of polysaccharides elaborated by the fermentative action of certain appropriate strains of *Leuconostoc mesenteroides* on a sucrose substrate. It is a glucose polymer in which the linkages between glucose units are almost entirely of the α-1:6 type. Its weight average molecular weight is in the 63 000 to 77 000 range. A 6% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 70 preparations.

Storage. Crystals may form in solutions of dextran if they are stored at low temperatures. These may be redissolved by warming for a short time.

Uses and Administration

Dextran 70 is a plasma volume expander used in the management of hypovolaemic shock (p. 1279.3). As a 6% solution dextran 70 exerts a colloidal osmotic pressure similar to that of plasma proteins and thus produces less

expansion of plasma volume than dextrans of a lower molecular weight, although the expansion may have a longer duration because of less rapid renal excretion. Dextran 70 also reduces blood viscosity, interferes with fibrin polymerisation, has an antiplatelet effect, and inhibits sludging or aggregation of red blood cells. It may be used in the prophylaxis of postoperative thromboembolic disorders (p. 1274.1).

Dextran 70 is given by intravenous infusion as a 6% solution, usually in sodium chloride 0.9% or glucose 5%.

Doses depend on the severity of the plasma loss and on the degree of haemoconcentration.

In **shock**, the usual initial dose for rapid expansion of plasma volume is 500 to 1000 mL infused at a rate of 20 to 40 mL/minute. A suggested maximum dose is 20 mL/kg during the first 24-hour period and 10 mL/kg per day thereafter; treatment should not continue for longer than 3 days. Patients may also require blood, coagulation factors, and electrolytes. A hypertonic solution of 6% dextran 70 in sodium chloride 7.5% is also available for use as a plasma expander, given in a single intravenous dose of 250 mL over 2 to 5 minutes, followed by isotonic fluids as required.

For the prophylaxis of pulmonary embolism or venous **thrombosis** in moderate- to high-risk patients undergoing surgery, a dose of 500 to 1000 mL may be given over 4 to 6 hours either during or immediately after surgery. A dose of 500 mL should be given on the next day and in high-risk patients on subsequent alternate days for up to 2 weeks after the operation.

A 32% solution of dextran 70 has been instilled into the uterus in a dose of 50 to 100 mL as a rinsing and dilatation fluid to aid **hysteroscopy**.

Dextran 70 is also an ingredient of artificial tears.

Hypertonic solutions. There is some evidence to suggest that hypertonic solutions of dextran 70 in sodium chloride 7.5% may be an effective treatment option for hypovolaemic shock resulting from trauma.[1,2]

1. Wade CE, *et al.* Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. *Surgery* 1997; 122: 609–16.
2. Alpar EK, Killampalli VV. Effects of hypertonic dextran in hypovolaemic shock: a prospective clinical trial. *Injury* 2004; 35: 500–506.

Adverse Effects and Treatment

Infusions of dextrans may occasionally produce hypersensitivity reactions such as fever, nasal congestion, joint pains, urticaria, hypotension, and bronchospasm. Severe anaphylactic reactions occur rarely and may be fatal. Dextran-reactive antibodies have been detected in patients who have not previously received dextran. This may possibly be in response to dietary or bacterial polysaccharides. Nausea and vomiting have also been reported. These reactions are treated symptomatically after withdrawal of the dextran.

Dextran 1 (p. 1137.3) may be used to block the formation of dextran-reactive antibodies and hence the hypersensitivity reactions.

Effects on the blood. A syndrome of acute hypotension, pulmonary oedema, coagulopathy, and anaemia, has occurred after the intra-uterine instillation of 32% solution of dextran 70 for hysteroscopy.[1] The volumes of solution that were used in 10 reported cases ranged from 300 to 1200 mL, and these large volumes may have contributed to the intravascular absorption of dextran. The pathogenesis and role of dextran in this syndrome are unclear but suggestions have included acute volume overload, direct alveolar endothelial damage, and release of tissue factors that promote fibrinolysis and a consumptive coagulopathy.

1. Ellingson TL, Aboulafia DM. Dextran syndrome: acute hypotension, noncardiogenic pulmonary edema, anemia, and coagulopathy following hysteroscopic surgery using 32% dextran 70. *Chest* 1997; 111: 513–18.

Effects on the kidneys. For a report of acute renal failure associated with use of dextran 70, see Dextran 40, p. 1138.2.

Hypersensitivity. In a retrospective study of allergic reactions to dextran 40 and dextran 70 reported in Sweden from 1970 to 1979,[1] there were 478 reports of reactions, 458 of which were considered to be due to dextran, out of 1 365 266 infusions given. There was a male to female ratio of 1.5 to 1 for all reactions and a ratio of 3 to 1 for the most severe reactions. The mean age of the patients was higher in those with severe reactions. Of the 28 fatal reactions, 27 occurred within 5 minutes of the start of the infusion and 25 when less than 25 mL had been infused. Three of the fatal reactions occurred after a test dose of only 0.5 to 1 mL and it was strongly recommended that such test doses should not be used.

An anaphylactic reaction has also been reported[2] more than 75 minutes after intraperitoneal instillation. After successful symptomatic treatment symptoms recurred 20 minutes later, due to slow absorption of dextran from the peritoneal cavity. No further reaction occurred after removal of 200 mL of intraperitoneal fluid by culdocentesis.

Anaphylactoid reactions after BCG vaccination have been attributed to hypersensitivity to dextran in the formulation.[3]

The use of dextran 1 for the prevention of hypersensitivity reactions is discussed under that monograph (p. 1137.3).

1. Ljungström K-G, *et al.* Adverse reactions to dextran in Sweden 1970–1979. *Acta Chir Scand* 1983; 149: 253–62.
2. Botten M, *et al.* Recurrent anaphylactic reaction to intraperitoneal dextran 75 used for prevention of postsurgical adhesions. *Obstet Gynecol* 1983; 61: 755–7.
3. Rudin C, *et al.* Anaphylactoid reaction to BCG vaccine containing high molecular weight dextran. *Eur J Pediatr* 1995; 154: 941–2.

Precautions

Dextran infusions produce a progressive dilution of oxygen-carrying capacity, coagulation factors, and plasma proteins and may overload the circulation. They are therefore contra-indicated in patients with severe heart failure, bleeding disorders such as hypofibrinogenaemia or thrombocytopenia, or renal failure and should be used with caution in patients with renal impairment, haemorrhage, chronic liver disease, or those at risk of developing pulmonary oedema or heart failure. Central venous pressure should be monitored during the initial period of infusion to detect fluid overload. Also patients should be watched closely during the early part of the infusion period, and the infusion stopped immediately if signs of anaphylactic reactions appear. Infusions should also be stopped if there are signs of oliguria or renal failure. The haematocrit should not be allowed to fall below 30% and all patients should be observed for early signs of bleeding complications. The bleeding time may be increased especially in patients receiving large volumes of dextrans. Deficiency of coagulation factors should be corrected and fluid and electrolyte balance maintained. Dehydration should be corrected before or at least during dextran infusions, in order to maintain an adequate urine flow.

The anticoagulant effect of heparin may be enhanced by dextran.

The higher molecular weight dextrans may interfere with blood grouping and cross-matching of blood, while the lower molecular weight dextrans may interfere with some methods. Therefore, whenever possible, a sample of blood should be collected before giving the dextran infusion and kept frozen in case such tests become necessary.

The presence of dextran may interfere with the determination of glucose, bilirubin, or protein in blood.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dextrans as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

After intravenous infusion dextrans with a molecular weight of less than 50 000 are excreted unchanged by the kidney. Dextrans with a molecular weight greater than 50 000 are slowly metabolised to glucose. Small amounts of dextrans are excreted into the gastrointestinal tract and eliminated in the faeces.

About 50% of dextran 70 is excreted unchanged in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Hyskon†; ***Canad.***: LMD; ***China***: Run Qi (润齐); ***Denm.***: Macrodex; RescueFlow; ***Fin.***: RescueFlow; ***Fr.***: RescueFlow†; ***Ital.***: Plander; ***Neth.***: RescueFlow†; ***Norw.***: Macrodex; RescueFlow; ***Port.***: Neodextril 70; ***S. Afr.***: Macrodex†; RescueFlow; ***Swed.***: Macrodex; RescueFlow; ***Switz.***: Dialens†; ***Turk.***: Macrodex; RescueFlow; ***UK***: Gentran 70; RescueFlow; ***USA***: Gentran 70†; Hyskon; Macrodex†; ***Venez.***: Lacridos; Lacrimart; Lagrimas Artificiales.

Multi-ingredient Preparations. ***Arg.***: Alcon Lagrimas; Kalopsis Lagrimas; Phoenix Lagrimas; Tears Naturale Forte; Tears Naturale†; Visine Plus; ***Austral.***: Bion Tears; Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Belg.***: Alcon Adequad; Lacrystat; Tears Naturale; ***Braz.***: Lacribell; Lacrima Plus; Opti-Tears; Trisorb; ***Canad.***: Artificial Tears†; Bion Tears; Tears Naturale Forte; Tears Naturale; Visine Advance Triple Action; ***Chile***: Kliner; Lagrimas Artificiales; Naphtears; Nico Drops; Nicotears; Novo-Tears; Tears Naturale; ***China***: Bion Tears (倍然); Tears Naturale Forte (新泪然); Tears Naturale II (泪然II); ***Cz.***: Tears Naturale; ***Denm.***: Dacriosol; ***Gr.***: Tearprol; Tears Naturale; ***Hong Kong***: Bion Tears; Tears Naturale Forte; Tears Naturale; ***Hung.***: Dacrolux; Tears Naturale; ***Indon.***: Isotic Tearin; Tears Naturale II; Tears; ***Irl.***: Physiotears†; Tears Naturale; ***Israel***: Tears Natural; ***Ital.***: Dacriosol; ***Malaysia***: Bion Tears; Dacrolux; Tears Naturale; ***Mex.***: Lacrima Plus; Naphtears; Naturalag; Tears Naturale; Visine Extra; ***Neth.***: Duratears; Tears Naturale; ***Norw.***: Tears Naturale; ***NZ***: Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Philipp.***: Gentle Tears; Tears Naturale; ***Pol.***: Tears Naturale; ***Rus.***: Tears Naturale (Слеза Натуральная); ***S. Afr.***: Tears Naturale; ***Singapore***: Bion Tears; Tears Naturale; ***Spain***: Dacrolux; Tears Humectante; ***Swed.***: Bion Tears; ***Switz.***: Tears Naturale; ***Thai.***: Bion Tears†; Opsar Tears; Tears Naturale; ***Turk.***: Dacrolux; Tears Naturale; ***UK***: Tears Naturale; ***Ukr.***: Tears Naturale (Штучні Сльози)†; ***USA***: Advanced Relief Visine; Bion Tears; Lacri-Tears; LubriTears; Moisture Drops; Nature's Tears; Ocucoat†; Tears Naturale; Tears Renewed†; ***Venez.***: Opti-Fresh.

Pharmacopoeial Preparations

BP 2014: Dextran 70 Infusion;
USP 36: Dextran 70 in Dextrose Injection; Dextran 70 in Sodium Chloride Injection.

Dextran 75 *(BAN, USAN, rINN)* ⊗

Dextrán 75; Dextrano 75; Dextranum 75; Декстран 75.

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.
UNII — JY83SHX053.

Profile

Dextran 75 consists of dextrans (glucose polymers) of weight average molecular weight about 75 000 that are derived from the dextrans produced by the fermentation of sucrose by means of a certain strain of *Leuconostoc mesenteroides*.

Dextran 75 is a plasma volume expander with actions and uses similar to dextran 70 (p. 1138.3). It is given by intravenous infusion as a 6% solution in sodium chloride 0.9% or glucose 5%.

Ecallantide *(USAN, rINN)*

DX-88; Ecalantida; Écallantide; Ecallantidum; Экальнантид.
Human plasma kallikrein-inhibitor (synthetic protein).

CAS — 460738-38-9.
ATC — B06AC03.
ATC Vet — QB06AC03.
UNII — 5Q6TZN2HNM.

Uses and Administration

Ecallantide is a recombinant inhibitor of human plasma kallikrein. It reduces the conversion of high molecular weight kininogen to bradykinin and is used in the treatment of acute attacks of hereditary angioedema (p. 2485.2). Three subcutaneous doses of 10 mg are given as a single treatment; the 3 injection sites may be in the same or different anatomical areas (abdomen, thigh, or upper arm), but should be separated by at least 5 cm and away from the site of the attack. If the attack persists, a second dose of three 10-mg injections may be given within 24 hours.

Reviews.

1. Levy JH, O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Invest Drugs* 2006; 15: 1077–90.
2. Schneider L, *et al.* Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol* 2007; 120: 416–22.
3. Lehmann A. Ecallantide (DX-88), a plasma kallikrein inhibitor for the treatment of hereditary angioedema and the prevention of blood loss in on-pump cardiothoracic surgery. *Expert Opin Biol Ther* 2008; 8: 1187–99.

Adverse Effects and Precautions

Hypersensitivity reactions, including pruritus, rash, and urticaria, have occurred in patients given ecallantide. Anaphylaxis has also been reported, usually within 1 hour of dosing, and must be distinguished from hereditary angioedema, which has similar symptoms. Other adverse effects include headache, nausea, diarrhoea, and pyrexia. Injection site reactions such as pruritus, erythema, pain, irritation, urticaria, and bruising have also occurred.

Antibodies to ecallantide have been found in some patients, which may increase the risk of hypersensitivity reactions; the long-term effects of antibody formation are unknown.

References.

1. Caballero T, López-Serrano C. Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J Allergy Clin Immunol* 2006; 117: 476–7.

Pharmacokinetics

Peak plasma concentrations of ecallantide occur about 2 to 3 hours after a subcutaneous dose. It is excreted in the urine, and has an elimination half-life of about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel*: Kalbitor; *USA*: Kalbitor.

Eltrombopag *(rINN)*

Eltrombopagum; SB-497115; Элтромбопаг.
3′-[(2Z)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl]-2′-hydroxybiphenyl-3-carboxylic acid.
$C_{25}H_{22}N_4O_4$=442.5
CAS — 496775-61-2.
ATC — B02BX05.
ATC Vet — QB02BX05.
UNII — 5S6D65XJ9G.

Eltrombopag Olamine *(USAN, rINNM)*

Eltrombopag olamina; Eltrombopagum Olaminum; SB-497115-GR; Элтромбопаг Оламин.
3′-[(2Z)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl]-2′-hydroxybiphenyl-3-carboxylic acid compound with 2-aminoethanol (1:2).
$C_{25}H_{22}N_4O_4.2(C_2H_7NO)$=564.6
CAS — 496775-62-3.
ATC — B02BX05.
ATC Vet — QB02BX05.
UNII — 4U07F515LG.

Uses and Administration

Eltrombopag is a non-peptide thrombopoietin receptor agonist. It interacts with the receptor to produce an increase in platelet production. Eltrombopag is used to treat thrombocytopenia in patients with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura; p. 1606.1), who have not responded sufficiently to treatment with corticosteroids, immunoglobulins, or splenectomy and are at increased risk of bleeding. It is also used for thrombocytopenia in patients with chronic hepatitis C (p. 952.1) to allow the use of interferon-based therapy. Eltrombopag should not be used in an attempt to normalise platelet counts.

Eltrombopag is given as the olamine salt, but doses are expressed in terms of the free acid; 12.8 mg of eltrombopag olamine is equivalent to about 10 mg of eltrombopag.

In patients with chronic immune thrombocytopenia, the usual initial oral dose is equivalent to 50 mg of eltrombopag once daily, given on an empty stomach. A reduced dose of 25 mg once daily is recommended for patients of East Asian origin (e.g. Chinese). The dose may need to be reduced in patients with hepatic impairment (see below). The dose of eltrombopag should be adjusted to achieve and maintain a platelet count of at least 50×10^9 cells/litre, as necessary, to reduce the risk of bleeding. The effect of a dose change should be monitored for at least 2 weeks. The daily dose should not exceed 75 mg.

In patients with hepatitis C, an initial oral dose of eltrombopag 25 mg once daily is used; no dose reduction is needed for those of East Asian origin or with hepatic impairment (but see also Adverse Effects and Precautions, below, regarding hepatotoxicity risks in these patients). The dose may be adjusted in steps of 25 mg every 2 weeks until the platelet count allows antiviral therapy to be started, and then to avoid reductions of the interferon dose. The maximum recommended daily dose of eltrombopag is 100 mg. If antiviral therapy is stopped then eltrombopag treatment should also cease.

US licensed product information advises the following adjustments based on platelet counts.

- If the platelet count is *lower than* 50×10^9 *cells/litre* for at least 2 weeks, the daily dose should be increased by 25 mg. In patients with chronic immune thrombocytopenia eltrombopag should be discontinued if, after 4 weeks of treatment at the maximum dose, the platelet count has not risen to a level sufficient to avoid clinically important bleeding. (UK licensed information also suggests that in patients with hepatitis C, treatment should be stopped if there has been insufficient response after 2 weeks at the maximum dose.)
- If the count is *higher than* 200×10^9 *cells/litre* at any time, then the daily dose should be reduced by 25 mg. The effects of this and any subsequent dose adjustment, should be assessed after waiting 2 weeks.
- If the count is *higher than* 400×10^9 *cells/litre*, then eltrombopag should be withheld and platelet counts measured twice a week. Treatment may be restarted at the previous daily dose reduced by 25 mg, when the count has fallen below 150×10^9 cells/litre; for patients already taking 25 mg daily, treatment may be restarted at 12.5 mg once daily. If the count is higher than 400×10^9 cells/litre after 2 weeks at the lowest dose of eltrombopag, treatment should be permanently stopped.

Licensed product information in other countries may differ regarding the platelet count threshold at which dose adjustments should be made. For example, UK information advises that the dose should be reduced when the platelet count is higher than 100×10^9 cells/litre in patients with hepatitis C or 150×10^9 cells/litre in those with immune thrombocytopenia; and treatment withheld if the count is higher than 150×10^9 cells/litre in hepatitis C or 250×10^9 cells/litre in immune thrombocytopenia.

Liver function tests and full blood counts (including platelet counts and peripheral blood smears) must be monitored frequently during eltrombopag therapy. Blood tests should also be routinely monitored after stopping the drug. For further details on monitoring, see below.

Eltrombopag is also under investigation as a platelet growth factor for the management of oncology-related thrombocytopenia and in aplastic anaemia.

References.

1. McHutchison JG, *et al.* Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; 357: 2227–36.
2. Bussel JB, *et al.* Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; 357: 2237–47.
3. Tillmann HL, *et al.* Role of growth factors and thrombopoietic agents in the treatment of chronic hepatitis C. *Curr Gastroenterol Rep* 2009; 11: 5–14.
4. Bussel JB, *et al.* Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 373: 641–8.
5. Cheng G, *et al.* Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377: 393–402. Correction. *ibid.*: 640.
6. Garnock-Jones KP. Eltrombopag: a review of its use in treatment-refractory chronic primary immune thrombocytopenia. *Drugs* 2011; 71: 1333–53.
7. Zhang Y, Kolesar JM. Eltrombopag: an oral thrombopoietin receptor agonist for the treatment of idiopathic thrombocytopenic purpura. *Clin Ther* 2011; 33: 1560–76.
8. Olnes MJ, *et al.* Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *N Engl J Med* 2012; 367: 11–19. Correction. *ibid.*: 284.

Administration in hepatic impairment. Patients with chronic immune thrombocytopenia and hepatic impairment should start eltrombopag treatment at an oral dose of 25 mg once daily. Dose increases should only be made at intervals of at least 3 weeks. For patients of East Asian origin (e.g. Chinese) an initial dose of 12.5 or 25 mg once daily may be used; if it is then necessary to increase the dose, the lower dose of 12.5 mg should be increased to 25 mg daily before any further increases of 25 mg.

No dose adjustment is considered necessary in patients being treated for thrombocytopenia associated with hepatitis C who have hepatic impairment.

Adverse Effects and Precautions

The most common serious adverse effect of eltrombopag is haemorrhage, which usually occurs after stopping the drug. Bleeding problems such as epistaxis, gingival bleeding, and ecchymosis may also occur. Other common adverse effects include headache, insomnia, fatigue, arthralgia, myalgia, paraesthesia, peripheral oedema, rash, pruritus, alopecia, dry eye, and cataracts. Gastrointestinal disturbances have included dyspepsia, nausea, vomiting, diarrhoea, and constipation.

Eltrombopag may cause hepatotoxicity. Raised liver function tests including bilirubin have been reported, and should therefore be monitored carefully (see below). Caution is advised in patients with liver disease and a reduced initial dose is recommended for those with chronic immune thrombocytopenia. Most patients with chronic hepatitis C who are also receiving an interferon and ribavirin will develop indirect hyperbilirubinaemia; those with cirrhosis may also be at increased risk of hepatic decompensation and death.

Excessive increases in platelet counts with eltrombopag treatment may lead to thrombosis or thromboembolic complications. The drug should be used with caution in patients with known risk factors for thromboembolism. Patients with chronic liver disease are at increased risk of portal venous thrombosis in particular. Eltrombopag increases the risk for the development or progression of reticulin fibre deposition in the bone marrow, and a risk of bone marrow fibrosis with cytopenias has not been excluded. Monitoring of full blood count and peripheral blood smears is essential (see below).

Due to the way eltrombopag acts on haematopoietic cells, it may possibly increase the risk of haematological malignancies.

Effects on the cardiovascular system. A study[1] of eltrombopag in the treatment of thrombocytopenia due to chronic liver disease of various causes was stopped early because of an excessive number of cases of portal venous thrombosis in patients given the drug (patients had been given eltrombopag or placebo for 14 days before elective invasive surgery). Five of the 6 patients who developed thrombosis had platelet counts above 200×10^9 cells/litre. The manufacturer (*GSK, USA*) and the FDA issued a reminder that eltrombopag should be used with caution in patients with known risk factors for thromboembolism.[2]

1. Afdhal NH, *et al.* ELEVATE Study Group. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med* 2012; 367: 716–24.
2. FDA. Promacta (eltrombopag): portal venous system thromboses in study of patients with chronic liver disease (issued 12th May, 2010). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211756.htm (accessed 02/06/10)

Effects on the skin. Severe skin reactions, including maculopapular rash, erythroderma, and pruritus, have been described in 2 patients given eltrombopag. The reactions occurred 9 weeks and 3 months after starting the drug; the patients were managed symptomatically and eltrombopag was replaced by romiplostim. A third patient with mild rash and pruritus was treated with antihistamines and eltrombopag therapy continued.[1]

1. Meyer SC, *et al.* Severe cutaneous toxicity related to eltrombopag. *Br J Haematol* 2013; 160: 412–14.

Monitoring. *BLOOD.* A full blood count, including the platelet count and peripheral blood smears, must be assessed before starting eltrombopag, then monitored weekly during dose adjustment and monthly during stable therapy. The level of cellular morphologic abnormalities must be established before starting treatment, and eltrombopag should be stopped if new or worsening abnormalities or cytopenias develop. After stopping treatment, thrombocytopenia is likely to recur. As this may increase the risk of bleeding, full blood counts (including platelet counts) should be monitored every week for at least 4 weeks after eltrombopag is stopped.

EYES. Licensed product information recommends that an eye examination should be performed before starting eltrombopag and then regularly during treatment, for signs and symptoms of cataract formation.

LIVER. Liver function including bilirubin levels should be measured before starting eltrombopag and then every 2 weeks while the dose is adjusted; once the dose is established, monthly monitoring is recommended. Tests should be repeated within 3 to 5 days if found to be abnormal and, if this is confirmed, liver function should be monitored every week. Eltrombopag should be stopped if alanine aminotransferase levels increase to ≥3 times above the upper limit of normal, or to ≥3 times above baseline for patients with pre-existing elevations, and these increases are:

- progressive or
- persistent for 4 weeks or longer or
- accompanied by increased direct bilirubin or by signs and symptoms of hepatic injury or decompensation

Interactions

The absorption of eltrombopag is reduced by polyvalent cations such as aluminium, calcium, iron, magnesium, selenium, and zinc. To avoid subtherapeutic serum concentrations, eltrombopag should not be taken within 4 hours of some foods such as milk and dairy products, mineral supplements, antacids or other preparations containing such cations. The use of lopinavir-ritonavir can reduce plasma concentrations of eltrombopag, and platelet counts should be closely monitored when lopinavir-ritonavir therapy is started or stopped.

Eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and breast cancer resistance protein (BCRP), and may increase exposure to drugs that are substrates of these; it has been reported to increase plasma concentrations of rosuvastatin.

References.

1. Williams DD, *et al.* Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies. *Clin Ther* 2009; 31: 764–76.
2. Wire MB, *et al.* Assessment of the pharmacokinetic interaction between eltrombopag and lopinavir-ritonavir in healthy adult subjects. *Antimicrob Agents Chemother* 2012; 56: 2846–51.

Pharmacokinetics

Eltrombopag is absorbed from the gastrointestinal tract and peak plasma concentration occur 2 to 6 hours after a dose. The concentration of eltrombopag in red blood cells is about 50 to 79% of the plasma concentration. It is highly bound to plasma proteins. Eltrombopag is extensively metabolised, undergoing oxidative metabolism by the cytochrome P450 isoenzymes CYP1A2 and CYP 2C8, and glucuronidation by the UDP-glucuronosyltransferases UGT1A1 and UGT1A3. About 31% of a dose is eliminated in the urine as metabolites, and about 59% in the faeces; 20% of a dose is eliminated unchanged in the faeces. The elimination half-life is about 26 to 35 hours in patients with immune thrombocytopenia.

After adjustment for body-weight, plasma-eltrombopag exposure is found to be about 50% higher in some patients

of East Asian origin (e.g. Japanese, Chinese, Taiwanese, and Korean) compared with Caucasian patients.

References.
1. Bauman JW, *et al.* Effect of hepatic or renal impairment on eltrombopag pharmacokinetics. *J Clin Pharmacol* 2011; **51**: 739–50.
2. Gibiansky E, *et al.* Population pharmacokinetics of eltrombopag in healthy subjects and patients with chronic idiopathic thrombocytopenic purpura. *J Clin Pharmacol* 2011; **51**: 842–56.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Revolade; ***Austria***: Revolade; ***Belg.***: Revolade; ***Braz.***: Revolade; ***Cz.***: Revolade; ***Denm.***: Revolade; ***Fr.***: Revolade; ***Ger.***: Revolade; ***Gr.***: Revolade; ***Irl.***: Revolade; ***Israel***: Revolade; ***Jpn***: Revolade; ***Norw.***: Revolade; ***NZ***: Revolade; ***Pol.***: Revolade; ***Port.***: Revolade; ***Rus.***: Revolade (Революйд); ***Spain***: Revolade; ***Swed.***: Revolade; ***Switz.***: Revolade; ***Thai.***: Revolade; ***Turk.***: Revolade; ***UK***: Revolade; ***Ukr.***: Revolade (Революл); ***USA***: Promacta.

Epoetins ⊗

Epoetinas; Эпоэтины.
ATC — B03XA01.
ATC Vet — QB03XA01.

Description. Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor produced mainly in the kidneys.

Erythropoietin for clinical use is produced by recombinant DNA technology and the name epoetin is often applied to such material. Epoetin alfa, epoetin beta, epoetin gamma, epoetin lambda, epoetin omega, epoetin theta, and epoetin zeta are recombinant human erythropoietins derived from a cloned human erythropoietin gene. All have the same 165 amino acid sequence but differ in the glycosylation pattern. Epoetin delta is a recombinant human erythropoietin derived from a genetically engineered continuous human cell line. It has the same amino acid sequence and glycosylation pattern as human erythropoietin.

Pharmacopoeias. *Eur.* (see p. vii) includes Erythropoietin Concentrated Solution.

Ph. Eur. 8: (Erythropoietin Concentrated Solution). A clear or slightly turbid colourless solution, containing 0.05 to 1% of glycoproteins indistinguishable from naturally occurring human erythropoietin in terms of amino acid sequence and glycosylation pattern. It has a potency of not less than 100 000 units per mg of active substance. Store in airtight containers below -20 degrees and avoid repeated freezing and thawing.

Epoetin Alfa *(BAN, USAN, rINN)* ⊗

EPO; Epoetina alfa; Époétine Alfa; Epoetinum Alfa; Эпоэтин Альфа.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α.
CAS — 113427-24-0.
ATC — B03XA01.
ATC Vet — QB03XA01.
UNII — 64FS3BFH5W.

NOTE. The name epoetin alfa has been permitted in some commercial preparations containing epoetin lambda, and some literature may use the term epoetin alfa to represent epoetin lambda (see below).

Epoetin Beta *(BAN, USAN, rINN)* ⊗

BM-06.019; EPOCH; Epoetina beta; Époétine Bêta; Epoetinum Beta; Эпоэтин Бета.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β.
CAS — 122312-54-3.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Delta *(BAN, USAN, rINN)* ⊗

Epoetina delta; Époétine Delta; Epoetinum Delta; GA-EPO; HMR-4396; Эпоэтин Дельта.
1–165-Erythropoietin (human HMR4396), glycoform δ.
CAS — 261356-80-3.
ATC — B03XA01.
ATC Vet — QB03XA01.
UNII — 474EI5756Y.

Epoetin Gamma *(BAN, rINN)* ⊗

BI-71.052; Epoetina gamma; Époétine Gamma; Epoetinum Gamma; Эпоэтин Гамма.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform γ.
CAS — 130455-76-4.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Kappa *(rINN)* ⊗

Epoetina Kappa; Époétine Kappa; Epoetinum Kappa; JR-013; Эпоэтин Каппа.
1–165-Erythropoietin (human JR-013), glycoform κ.
CAS — 879555-13-2.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Lambda ⊗

HX-575.
ATC — B03XA01.
ATC Vet — QB03XA01.

NOTE. Epoetin lambda was developed as a biosimilar product to epoetin alfa, but glycosylation patterns differ between the two forms. The name epoetin alfa has been permitted in some commercial preparations containing epoetin lambda, and some literature may use the term epoetin alfa to represent epoetin lambda.

Epoetin Omega *(rINN)* ⊗

Epoetina omega; Époétine Oméga; Epoetinum Omega; Эпоэтин Омега.
1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform ω.
CAS — 148363-16-0.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Theta *(BAN, rINN)* ⊗

Epoetina Zeta; Époétine Thêta; Epoetinum Theta; Эпоэтин Тета.
Human erythropoietin-(1–165)-peptide, glycoform θ.
CAS — 762263-14-9.
ATC — B03XA01.
ATC Vet — QB03XA01.

NOTE. In Spanish, epoetin theta is given the name Epoetina Zeta (*rINN*), which should not be confused with Epoetin Zeta (below).

Epoetin Zeta *(rINN)* ⊗

Epoetina dseta; Époétine Zêta; Epoetinum Zeta; Эпоэтин Дзета.
1–165-Erythropoietin (human clone B03XA01), glycoform ζ.
CAS — 604802-70-2.
ATC — B03XA01.
ATC Vet — QB03XA01.

NOTE. In Spanish, the name Epoetina Dseta (*rINN*) is used for epoetin zeta. These terms should not be confused with the Spanish name Epoetina Zeta (*rINN*), which is used for Epoetin Theta (above).

Stability. Proprietary preparations of recombinant human erythropoietin may contain albumin or amino acids for stability. Use in neonates may necessitate making very dilute solutions. A study of the stability of epoetin alfa in various intravenous fluids[1] found that a minimum of 0.05% protein was required to prevent loss of drug from solutions containing epoetin alfa 0.1 units/mL. In another study,[2] 0.0125% albumin was sufficient to prevent loss of drug from a solution containing epoetin alfa 100 units/mL. Epoetin alfa was stable for up to 24 hours in a solution for enteral use in neonates, formulated to mimic amniotic fluid, which also contained filgrastim and electrolytes.[3] Epoetin alfa and filgrastim were stable for at least 24 hours when refrigerated and for at least 3 weeks when frozen. At room temperature epoetin alfa was stable for 24 hours and filgrastim was stable for 18 hours. Lowered epoetin alfa concentrations were thought to be due to adsorption to the plastic infusion bag or tubing, and this was overcome by priming the tubing.

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2. Widness JA, Schmidt RL. Comment: epoetin alfa loss with NaCl 0.9% dilution. *Ann Pharmacother* 1996; **30**: 1501–2.
3. Calhoun DA, *et al.* Stability of filgrastim and epoetin alfa in a system designed for enteral administration in neonates. *Ann Pharmacother* 2000; **34**: 1257–61.

Uses and Administration

Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor. It is secreted mainly by the kidneys, although a small amount is produced in extrarenal sites such as the liver. Erythropoietin regulates erythropoiesis by stimulating the differentiation and proliferation of erythroid precursors, the release of reticulocytes into the circulation, and the synthesis of cellular haemoglobin. The release of erythropoietin is promoted by hypoxia or anaemia, and up to 1000 times the normal serum-erythropoietin concentration may be reached under these conditions; this response may be impaired in some disease states such as chronic renal failure. The haematological response to erythropoietin is reduced if there is an inadequate supply of iron. For an outline of blood cell formation in general and average cell counts in adults see Haematopoiesis, p. 1121.1.

Epoetins alfa, beta, lambda, theta, and zeta are recombinant human erythropoietins available for clinical use that have the same pharmacological actions as endogenous erythropoietin. They are used in the management of symptomatic anaemia associated with chronic renal failure in dialysis and predialysis patients; they may reduce or obviate the need for blood transfusions in these patients. Epoetins alfa, beta, lambda, theta, and zeta are also used in the management of chemotherapy-induced anaemia in patients with non-myeloid malignant disease. Epoetin alfa is used in zidovudine-related anaemia in HIV-positive patients. Epoetin beta is used in the prevention of anaemia of prematurity. Epoetins are also being evaluated in the management of normocytic-normochromic anaemias of various other causes (see p. 1142.3). In all patients, iron status should be monitored and supplementation provided if necessary.

Epoetins alfa, beta, lambda, and zeta may also be used in patients with moderate anaemia (but no iron deficiency) before elective surgery to increase the yield of blood collected for autologous blood transfusion. Epoetin alfa and lambda may also be used in such patients to reduce the need for allogeneic blood transfusion.

In the management of **anaemia of chronic renal failure** epoetins may be given intravenously or subcutaneously. For haemodialysis patients the dose of epoetin should be given intravenously because of the risk of pure red cell aplasia reported with subcutaneous use (see Effects on the Blood, p. 1143.3); it is usually given during or at the end of the dialysis session using the dialysis vascular access, although licensed product information for epoetin lambda recommends that it should always be administered after completion of dialysis. For predialysis and peritoneal dialysis patients, in whom intravenous access is not readily available, doses should be given subcutaneously. The aim of treatment is to use the lowest dose necessary to reduce the need for blood transfusion. A target haemoglobin range of 10 to 12 g per 100 mL, or to increase the haematocrit to 30 to 36%, has been used, but US licensed product information now recommends that epoetin therapy may be considered when the haemoglobin concentration is less than 10 g per 100 mL, and to reduce the dose or stop therapy if the concentration exceeds 10 g per 100 mL in patients not on dialysis or when it approaches or exceeds 11 g per 100 mL in patients on dialysis (see also Haematocrit and Haemoglobin, under Precautions, p. 1144.3). The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 1 g per 100 mL in any 2-week period, or 2 g per 100 mL over 4 weeks, is suggested.

Epoetin alfa, lambda, or ***zeta*** may be given by intravenous injection over at least 1 to 5 minutes; a slower intravenous injection is preferred in patients who have flu-like symptoms as adverse effects. Epoetin alfa or zeta may also be given subcutaneously.

- In predialysis and haemodialysis patients, a recommended initial dose of epoetin alfa, lambda, or zeta is 50 international units/kg three times weekly. For epoetin alfa, a higher initial dose of 50 to 100 units/kg three times weekly has been suggested in the US licensed product information.
- Doses may be increased at 4-week intervals in increments of 25 units/kg until the target is reached.
- In patients on peritoneal dialysis an initial dose of epoetin alfa or zeta 50 units/kg given twice weekly may be used.

Once the target haemoglobin is reached, doses of epoetin alfa, lambda, or zeta may need to be adjusted for maintenance therapy.

- In predialysis patients the usual total weekly dose of epoetin alfa or zeta is 50 to 100 units/kg given in three divided doses. A total weekly dose of 600 units/kg should not be exceeded.
- In haemodialysis patients the usual weekly dose of epoetin alfa, lambda, or zeta is between 75 and 300 units/kg given in three divided doses.
- In patients on peritoneal dialysis, the usual weekly dose of epoetin alfa or zeta is 50 to 100 units/kg given in two divided doses.

Epoetin beta is used similarly in the management of anaemia of chronic renal failure in dialysis and predialysis patients. It may be given subcutaneously or by intravenous injection over 2 minutes. The following dosages may be used in adults and children.

- For subcutaneous injection the initial dose is 60 units/kg weekly for 4 weeks; the total weekly dose may be divided to be given in daily doses or three times a week.
- For intravenous injection the initial dose is 40 units/kg three times weekly for 4 weeks; the dose may then be increased to 80 units/kg three times weekly.
- Thereafter the dose of epoetin beta may be increased at 4-week intervals, for both subcutaneous and intravenous injection; the increment should be equivalent to 60 units/kg weekly given in divided doses as outlined above, until the target haemoglobin concentration or haematocrit is reached. A total weekly dose of 720 units/kg of epoetin beta should not be exceeded.

For maintenance, the dose is halved initially and then adjusted every 1 to 2 weeks according to response. The weekly subcutaneous maintenance dose may be divided into 1, 3, or 7 doses; in patients stabilised on a once-weekly dose, it may be possible to adjust to a single dose every 2 weeks.

Epoetin theta is also given intravenously or subcutaneously in the management of anaemia of chronic renal failure.

- For subcutaneous injection the initial dose is 20 units/kg three times weekly for 4 weeks; the dose may then be increased, if necessary, to 40 units/kg three times weekly.
- For intravenous injection the initial dose is 40 units/kg three times weekly for 4 weeks; the dose may then be increased, if necessary, to 80 units/kg three times weekly.
- Thereafter the dose of epoetin theta, for both subcutaneous and intravenous injection, may be increased in steps of 25% of the previous dose at monthly intervals until the target haemoglobin concentration is reached. A total weekly dose of 700 units/kg should not be exceeded.

For maintenance, the dose should be adjusted as required. The weekly subcutaneous maintenance dose may be given in a single weekly dose or 3 divided doses. For intravenous dosing, the total weekly dose may be given in 2 or 3 divided doses.

Epoetins may be used for treating symptomatic chemotherapy-associated anaemia in patients with **non-myeloid malignant disease**. However, US licensed product information for epoetin alfa cautions that it is not indicated when the anticipated outcome is cure, because of the potential impact of epoetin therapy on progression-free and overall survival. See also Anaemias, below, for restrictions on the prescribing of epoetins in the USA for patients with cancer. Epoetin alfa, beta, lambda, theta, or zeta may be given by subcutaneous injection, usually when the haemoglobin concentration has fallen to 10 g or lower per 100 mL. The rise in haemoglobin should be gradual; a rate not exceeding 1 g per 100 mL in any 2-week period, or 2 g per 100 mL over 4 weeks, and a target haemoglobin concentration of 10 to 12 g per 100 mL, are suggested.

- ***Epoetin alfa, lambda,*** or ***zeta*** may be given in an initial dose of 150 units/kg three times weekly; epoetin alfa or zeta may also be given in a dose of 450 units/kg once weekly. The dose may be increased after 4 weeks, if necessary, to 300 units/kg three times weekly. Alternatively, epoetin alfa may be given in a once-weekly dose of 40 000 units, which may be increased to 60 000 units after 4 weeks if necessary. If the response is still inadequate after 4 weeks at the higher dose, treatment should be stopped.
- ***Epoetin beta*** may be given in an initial dose of 30 000 units (about 450 units/kg) weekly, as a single dose or divided into 3 to 7 doses. The dose may be doubled after 4 weeks if necessary, but treatment should be stopped if the response is still inadequate after 4 weeks at the higher dose. The total weekly dose should not exceed 60 000 units.
- ***Epoetin theta*** may be given in an initial dose of 20 000 units once weekly. The dose may be increased after 4 weeks, if necessary, to 40 000 units weekly. If the response is still inadequate after 4 weeks at this dose, it may be increased to a maximum weekly dose of 60 000 units. However, treatment should be stopped if the response is still inadequate after 12 weeks of therapy.

Once the desired haemoglobin concentration has been reached, the dose of epoetin alfa may be reduced by 25% for maintenance therapy, and adjusted as necessary; the dose of epoetin beta or zeta may be reduced by 25 to 50%. Epoetins should be stopped after the end of chemotherapy, but may be continued for up to one month in the UK.

In **HIV-positive patients** on zidovudine therapy, epoetin alfa may be beneficial if the endogenous serum-erythropoietin concentration is 500 milliunits/mL or less. Epoetin alfa is given by subcutaneous or intravenous injection in an initial dose of 100 units/kg three times weekly for 8 weeks. The dose may then be increased every 4 to 8 weeks by 50 to 100 units/kg according to response. However, patients are unlikely to benefit from doses above 300 units/kg three times weekly if this dose has failed to elicit a satisfactory response. The haemoglobin concentration should not be allowed to exceed 12 g per 100 mL.

To increase the yield of **autologous blood** for transfusion, epoetin alfa, beta, or zeta may be used with iron supplementation in patients with mild to moderate anaemia (haemoglobin 10 to 13 g per 100 mL or haematocrit 33 to 39%). Epoetin lambda may be used similarly. The dose depends on the volume of blood required for collection and on factors such as the patient's whole blood volume and haematocrit. At the time of donating blood, the epoetin should be given after the donation procedure. Suggested regimens are:

- ***epoetin alfa*** or ***zeta*** 600 units/kg given intravenously twice weekly starting 3 weeks before surgery
- ***epoetin lambda*** 300 to 600 units/kg given intravenously twice weekly starting 3 weeks before surgery
- 200 to 800 units/kg of ***epoetin beta*** intravenously, or 150 to 600 units/kg subcutaneously, twice weekly for 4 weeks before surgery

To reduce the need for **allogeneic blood transfusion**, epoetin alfa or lambda may be given in a dose of 600 units/kg subcutaneously once weekly starting 3 weeks before surgery, with a fourth dose given on the day of surgery. Alternatively, when the time before surgery is short, 300 units/kg subcutaneously daily may be given for 10 days before surgery, on the day of surgery, and for 4 days after. All patients should be given adequate iron supplementation, and epoetin treatment should be stopped if the haemoglobin concentration reaches 15 g per 100 mL or higher.

For the use of epoetins in **children**, see below.

Reviews.

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Administration in children. Epoetins are used in children for the management of anaemia associated with chronic renal failure and chemotherapy, and general advice about the rates of administration and rise in haemoglobin, and stopping epoetin therapy after chemotherapy, is similar to that given for adults (see p. 1141.2). However, some licensed product information suggests a lower haemoglobin target range for children than for adults, as described below. Epoetin beta may also be used for the prevention of anaemia of prematurity (see also Anaemias, below).

In the management of **anaemia of chronic renal failure**, epoetins are generally given intravenously to children on haemodialysis.

- The initial dose of epoetin alfa or zeta is 50 units/kg three times weekly. The dose may be increased at 4-week intervals in increments of 25 units/kg until a target haemoglobin concentration of 9.5 to 11 g per 100 mL is reached.

The usual total weekly maintenance dose given in three divided doses is:

- 225 to 450 units/kg for those weighing less than 10 kg
- 180 to 450 units/kg for those weighing 10 to 30 kg
- 90 to 300 units/kg for those weighing over 30 kg

Epoetin beta is given in similar unit/kg doses to those used for adults (see p. 1141.2).

In the management of symptomatic chemotherapy-associated anaemia in children with **non-myeloid malignant disease**, epoetin alfa may be given intravenously in a single weekly dose of 600 units/kg (to a maximum of 40 000 units). The dose may be increased if necessary after 4 weeks to 900 units/kg (maximum 60 000 units).

In the prevention of **anaemia of prematurity**, epoetin beta is given to neonates with a birth-weight of 750 to 1500 g and a gestational age of less than 34 weeks. A subcutaneous dose of 250 units/kg is given three times weekly. Treatment should be started as early as possible (preferably within 3 days of birth) and continued for 6 weeks.

Results from small studies suggest that once-weekly epoetin dosing regimens might be as effective as three times weekly dosing in premature infants, and that further investigation is warranted.[1,2] Although epoetin is generally given subcutaneously for anaemia of prematurity, other routes have been tried. Intravenous infusion in total parenteral nutrition solutions produced satisfactory results in a group of 20 neonates.[3] Enteral dosage in one small study[4] increased plasma-erythropoietin concentrations and peak reticulocyte counts, but in another larger study[5] it had no effect. For a warning about diluting epoetin solutions for use in neonates, see Stability, p. 1141.2.

1. Ohls RK, *et al.* A randomized, masked study of weekly erythropoietin dosing in preterm infants. *J Pediatr* 2012; 160: 790–5.
2. Vázquez López MÁ, *et al.* Comparison between one and three doses a week of recombinant erythropoietin in very low birth weight infants. *J Perinatol* 2011; 31: 118–24.
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Anaemias. Epoetins are used in normocytic-normochromic anaemias (p. 1123.1) associated with low endogenous erythropoietin concentrations.

Anaemia associated with *chronic renal disease* is mainly a result of inadequate production of erythropoietin in the kidney. Other factors that can contribute to the anaemia include iron deficiency, blood loss associated with dialysis, and severe hyperparathyroidism. The use of epoetins in the management of renal anaemia became well established[1,2] based on consistently good results for correction of anaemia and reports of improvement in quality of life.[1,3] In predialysis patients, epoetins were also reported to correct anaemia, reduce the requirement for blood transfusions, and improve quality of life and exercise capacity, but there may be increased hypertension[2,4] and it is unknown whether the need for dialysis is delayed.[4] However, the optimum haemoglobin range has not been established and higher targets have been associated with increased cardiovascular risks[5] (see also Haematocrit and Haemoglobin, under Precautions, p. 1144.3). An assessment of studies reporting effects on quality of life also concluded that there were high risks for bias because of selective reporting of outcomes.[5] Over 90% of patients with renal anaemia respond to treatment with epoetins.[1] Many factors can contribute to a poor response (see Precautions, p. 1144.2) and the patient should always be investigated and the cause corrected where possible. Common causes of inadequate response are iron deficiency, inflammatory disorders, chronic blood loss, hyperparathyroidism, and aluminium toxicity.[1,6]

Epoetins may be given intravenously or subcutaneously. Epoetin given subcutaneously produces lower but more sustained plasma concentrations and total weekly maintenance doses are reduced.[1,2,7] The subcutaneous route is generally used in predialysis patients and those on peritoneal dialysis,[1,2] partly because of the need to avoid venepuncture of veins that are likely to be needed for future haemodialysis access. While subcutaneous injection can also be used for haemodialysis patients, the intravenous route is preferred because of the rare risk of pure red cell aplasia reported with subcutaneous use[1] (see Effects on the Blood, p. 1143.3) and the ready availability of intravenous access. The dosage frequency may also be important in maximising the response to treatment, but may be influenced by the epoetin being used, route of administration, treatment phase, and patient preference. For example, giving epoetins 2 or 3 times a week may allow for a lower total weekly dose than once weekly, and may be more effective, but dosing once weekly may be more convenient for maintenance therapy.[1,2] A systematic review[8] concluded that there was no evidence to support one frequency over another in terms of maintaining target haemoglobin. See Uses and Administration, p. 1141.2, for examples of licensed doses, routes, and dose frequency for epoetins. Darbepoetin alfa (p. 1137.1) is given at longer dosage intervals than epoetins and there is no difference in weekly dosage requirements between subcutaneous and intravenous routes.[2,7]

Intraperitoneal use of epoetins has also been proposed and investigated.[9,10] However, this route is rarely used because the doses must be given into a dry abdomen,[1] dose requirements are generally higher than those for intravenous or subcutaneous use, and there is the potential for more frequent episodes of peritonitis.[1,2]

Blood transfusions are often used to treat *anaemia of prematurity*, and epoetins have been investigated as a means of reducing transfusion requirements. A systematic review[11] found that although epoetin reduced transfusion needs, the effect was only modest and there was considerable variation between studies. More selective reviews of very-low-birth-weight infants (less than 1500 g) also found modest reductions in transfusion requirements, whether epoetin was started within the first week of life[12] or after one week,[13] although transfusion requirements were unlikely to be eliminated completely. Response to the late use of epoetin was also found to be dose-dependent.[13] Another review[14] found evidence of an increase in the risk of retinopathy of prematurity in neonates treated with epoetins in the first week after birth. For most studies, this was a secondary study outcome and the effect could have been a chance finding; it was also considered possible that

high iron supplementation could have been a contributing factor.

Factors contributing to *cancer-related anaemia* include chemotherapy, radiotherapy, and the malignancy itself. Epoetin therapy can reduce the need for blood transfusions in cancer patients[15] and may improve quality of life.[16] Guidelines for the use of epoetins in chemotherapy-induced anaemia have been issued (see Anaemia, under Bone-marrow Depression, p. 731.1). There has, however, been some concern raised about the effect of epoetin therapy on patient survival. A placebo-controlled study of epoetin alfa to maintain normal haemoglobin concentrations (12 to 14 g per 100 mL) in patients receiving chemotherapy for metastatic breast cancer was terminated early when an increase in death was found in the epoetin group.[17] In another placebo-controlled study[18] of patients with head and neck cancer undergoing radiotherapy, epoetin beta was associated with correction of anaemia but poorer locoregional progression-free survival. In contrast, analysis of a study[19] in patients with lymphoproliferative malignancies found no effect of epoetin beta on patient survival. Subsequently, a study of the quality of life in anaemic patients with advanced non-small cell lung cancer was stopped early, when an unplanned safety analysis suggested a reduced overall survival in patients given epoetin alfa.[20] However, few epoetin studies were designed to assess their effects on tumour response and survival, although two later studies did aim to investigate these outcomes. One study in women treated with radiochemotherapy for advanced cervical cancer reported no positive correlation between haemoglobin increase and improvement in clinical outcomes, and could not draw a definite conclusion as to whether epoetin beta had an effect on disease progression or survival.[21] Another study, in women given chemotherapy for metastatic breast cancer, found that epoetin beta had no significant effect on overall survival.[22] Meta-analyses, which included these and other studies in cancer patients, found that epoetin or darbepoetin alfa therapy was associated with increased risks of venous thromboembolism[23] and death.[23,24] Studies to date have generally used haemoglobin targets of 12 g and above per 100 mL, and further information is needed on the benefits and risks associated with the lower targets now advised (see Uses and Administration, p. 1141.2). In response to these concerns, authorities have strengthened warnings in licensed product information regarding the use of epoetins and related products in patients with cancer. The FDA has directed[25] that epoetins and darbepoetin alfa can be prescribed for patients with cancer only by healthcare professionals who have completed specified training in the ESA APPRISE oncology program; in addition, they must only be dispensed by hospitals that are enrolled in the program. The MHRA has advised[26] that blood transfusion should be the preferred option for the management of anaemia in patients with cancer, particularly in those receiving adjuvant chemotherapy or who are being treated with curative intent. They also suggest that transfusion may be preferable in patients with advanced or metastatic cancer who have a good survival prognosis.

Epoetins are sometimes used to treat *anaemias from other causes*. Potential applications include zidovudine-induced anaemia in AIDS patients (see Effects on the Blood under Zidovudine, p. 1025.1), postpartum anaemia,[27,28] and anaemia of chronic diseases such as rheumatoid arthritis,[29,30] inflammatory bowel disease,[31-33] and chronic heart failure.[34] Epoetin treatment is also being investigated in critically ill patients,[35,36] but firm evidence of clinical benefit is lacking and routine use is not recommended.[37,38]

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25. FDA. Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen) darbepoetin alfa (marketed as Aranesp): safety announcement (issued 16th February, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109375.htm (accessed 16/08/10)
26. MHRA/CHM. Recombinant human erythropoietins: new recommendations for treatment of anaemia in cancer. *Drug Safety Update* 2008; **2** (1): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0230776&RevisionSelectionMethod=LatestReleased (accessed 15/08/08)
27. Kotto-Kome AC, *et al.* Effect of administering recombinant erythropoietin to women with postpartum anemia: a meta-analysis. *J Perinatol* 2004; **24**: 11–15.
28. Dodd J, *et al.* Treatment for women with postpartum iron deficiency anaemia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 27/10/05).
29. Peeters HRM, *et al.* Effect of recombinant human erythropoietin on anaemia and disease activity in patients with rheumatoid arthritis and anaemia of chronic disease: a randomised placebo controlled double blind 52 weeks clinical trial. *Ann Rheum Dis* 1996; **55**: 739–44.
30. Peeters HRM, *et al.* Recombinant human erythropoietin improves health-related quality of life in patients with rheumatoid arthritis and anaemia of chronic disease; utility measures correlate strongly with disease activity measures. *Rheumatol Int* 1999; **18**: 201–6.
31. Schreiber S, *et al.* Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996; **334**: 619–23.
32. Gasché C, *et al.* Intravenous iron and erythropoietin for anemia associated with Crohn disease: a randomized, controlled trial. *Ann Intern Med* 1997; **126**: 782–7.
33. Dohil R, *et al.* Recombinant human erythropoietin for treatment of anemia for chronic disease in children with Crohn's disease. *J Pediatr* 1998; **132**: 155–9.
34. van der Meer P, *et al.* Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. *Heart* 2009; **95**: 1309–14.
35. Corwin HL, *et al.* Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002; **288**: 2827–35.
36. Corwin HL, *et al.* EPO Critical Care Trials Group. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007; **357**: 965–76.
37. Zarychanski R, *et al.* Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. *CMAJ* 2007; **177**: 725–34.
38. Shermock KM, *et al.* Erythropoietic agents for anemia of critical illness. *Am J Health-Syst Pharm* 2008; **65**: 540–6.

Cardiovascular diseases. There is some interest[1] in the non-haematopoietic effects of erythropoietin, including protection from apoptosis, antioxidant activity, and pro-angiogenic effects. A possible role in the management of ischaemic stroke and myocardial infarction has been investigated.[2]

1. Arcasoy MO. The non-haematopoietic biological effects of erythropoietin. *Br J Haematol* 2008; **141**: 14–31.
2. van der Meer P, *et al.* Erythropoietin in cardiovascular diseases. *Eur Heart J* 2004; **25**: 285–91.

Perinatal brain injury. There is interest in the potential neuroprotective effects of epoetins,[1] particularly when given to neonates at risk of perinatal brain injury. A small study[2] showed that premature extremely low birth-weight infants with an elevated erythropoietin level due to epoetin use had higher mental development index scores at 18 to 22 months corrected age follow-up than those with lower erythropoietin concentrations, although psychomotor developmental index was not significantly different. Furthermore, it has also been seen that the neurodevelopmental outcomes, at age 10 to 13 years, of extremely preterm infants were significantly better in those who had received epoetin for the management of anaemia in the first weeks of life but only in those who had neonatal intraventricular haemorrhage.[3] Other studies[4,5] showed safety and tolerability of short-term therapy using doses higher than those generally used for anaemia of prematurity. Epoetin treatment might also reduce the risk of disability and improve neurodevelopmental outcomes in full-term neonates with mild to moderate hypoxic-ischaemic encephalopathy.[6,7]

1. McPherson RJ, Juul SE. Erythropoietin for infants with hypoxic-ischemic encephalopathy. *Curr Opin Pediatr* 2010; **22**: 139–45.
2. Bierer R, *et al.* Erythropoietin concentrations and neurodevelopmental outcome in preterm infants. *Pediatrics* 2006; **118**: e635–e640.
3. Neubauer A-P, *et al.* Erythropoietin improves neurodevelopmental outcome of extremely preterm infants. *Ann Neurol* 2010; **67**: 657–66.
4. Fauchère J-C, *et al.* An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. *Pediatrics* 2008; **122**: 375–82.
5. Juul SE, *et al.* A phase I/II trial of high-dose erythropoietin in extremely low birth weight infants: pharmacokinetics and safety. *Pediatrics* 2008; **122**: 383–91.
6. Zhu C, *et al.* Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. Abstract: *Pediatrics* 2009; **124**: 774. Full version: http://pediatrics.aappublications.org/content/124/2/e218.full.pdf (accessed 02/09/11)
7. Elmahdy H, *et al.* Human recombinant erythropoietin in asphyxia neonatorum: pilot trial. Abstract: *Pediatrics* 2010; **125**: 1054–5. Full version: http://pediatrics.aappublications.org/content/125/5/e1135.full.pdf (accessed 02/09/11)

Surgery. Concern over the safety of blood transfusions and the need to conserve blood supplies has led to interest in methods of reducing blood use in surgery. Recombinant human erythropoietin has been used to increase the number of units harvested for autologous transfusion[1] and to reduce transfusion requirements.[2-4] It has also been used as an alternative to blood transfusions in Jehovah's Witnesses.[5-8]

1. Goodnough LT, *et al.* Erythropoietin therapy. *N Engl J Med* 1997; **336**: 933–8.
2. Laupacis A, Fergusson D. Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. *Transfus Med* 1998; **8**: 309–17.
3. Barnshaw P. Blood conservation in orthopaedic surgery: the role of epoetin alfa. *Int Orthop* 2001; **25**: 273–8.
4. Alghamdi AA, *et al.* Does the use of erythropoietin reduce the risk of exposure to allogeneic blood transfusion in cardiac surgery? A systematic review and meta-analysis. *J Card Surg* 2006; **21**: 320–6.
5. Busuttil D, Copplestone A. Management of blood loss in Jehovah's Witnesses. *BMJ* 1995; **311**: 1115–16.
6. Cothren C, *et al.* Blood substitute and erythropoietin therapy in a severely injured Jehovah's Witness. *N Engl J Med* 2002; **346**: 1097–8.
7. Hashem B, Dillard TA. A 44-year-old Jehovah's Witness with life-threatening anemia from uterine bleeding. *Chest* 2004; **125**: 1151–4.
8. Holt RL, *et al.* Jehovah's Witnesses requiring complex urgent cardiothoracic surgery. *Ann Thorac Surg* 2004; **78**: 695–7.

Adverse Effects and Treatment

Adverse effects of epoetins include flu-like symptoms such as fever, chills, headache, arthralgias, myalgias, asthenia, dizziness, and tiredness, which occur especially at the start of treatment. Other effects include rashes, urticaria, nausea and vomiting, diarrhoea, hyperkalaemia, and reactions at the injection site. Severe hypersensitivity reactions have been reported rarely. Pure red cell aplasia associated with neutralising antibodies has been reported rarely in patients with chronic renal failure. It has also been rarely reported in patients with hepatitis C treated with ribavirin and interferon when also given epoetins. Epoetins are not approved for the management of anaemia associated with hepatitis C treatment. Modest increases in the platelet count within the normal range may occur during epoetin therapy.

Hypertension is common with the use of epoetins, particularly in patients with renal failure, and is associated with a rapid rise in haematocrit. Hypertensive crisis with encephalopathy and seizures has been reported, even in patients with initially normal or low blood pressure.

Reports of thromboembolism include myocardial ischaemia and infarction, transient ischaemic attacks and cerebrovascular accidents, deep-vein thrombosis, and pulmonary embolism. Shunt thromboses may occur in the arteriovenous fistulae of dialysis patients, and occlusion of the dialysis system is possible, due to an increased haematocrit.

General references.

1. Sowade B, *et al.* The safety of treatment with recombinant human erythropoietin in clinical use: a review of controlled studies. *Int J Mol Med* 1998; **1**: 303–14.
2. Vaziri ND. Mechanism of erythropoietin-induced hypertension. *Am J Kidney Dis* 1999; **33**: 821–8.
3. Smith KJ, *et al.* The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59**: 538–48.

Effects on the blood. The use of recombinant human erythropoietin has been associated with an increase in **thrombotic events**, including vascular access thrombosis in haemodialysis patients. Several mechanisms have been proposed for this increase such as increased blood viscosity, effects on proteins involved in coagulation, activation

of platelets and the endothelium, and a vasoconstrictor effect on vascular smooth muscle.[1]

Pure red cell aplasia has been reported rarely, in patients with chronic renal failure, after months to years of treatment with epoetin alfa; most patients have been found to have antibodies to epoetins.[2] There have also been a few cases in patients treated with epoetin beta.[3-5] A review[3] of cases reported between January 1988 and April 2004 found that the number peaked in 2001 and 2002, and decreased rapidly when changes were made to recommendations for storage, handling, and use of epoetin alfa preparations. The effect appeared to be brand specific[6-8] and associated particularly with the subcutaneous use of preparations containing polysorbate 80 as a stabiliser.[9] Other possible causes have been proposed including contamination with silicone lubricant used in pre-filled syringes or release of organic compounds from rubber plungers.[10] Subsequently, manufacturers have reported that cases of red cell aplasia with neutralising antibodies have also occurred in chronic renal failure patients treated with subcutaneous darbepoetin alfa.[11] They also warn that because of cross-reactivity, patients who develop antibody-mediated anaemia with either an epoetin or darbepoetin alfa should not be swapped to another erythropoietic protein.

Epoetin-induced red cell aplasia has been managed with withdrawal of the epoetin and treatment with immunosuppressants including corticosteroids, cyclophosphamide, and ciclosporin. Intravenous normal immunoglobulin has also been used. Kidney transplantation is reported to bring about a rapid recovery.[10,12]

1. Smith KJ, *et al.* The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59**: 538–48.
2. Casadevall N, *et al.* Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; **346**: 469–75.
3. Krüger A, *et al.* PRCA in a patient treated with epoetin beta. *Nephrol Dial Transplant* 2003; **18**: 1033–4.
4. Tolman C, *et al.* Four cases of pure red cell aplasia secondary to epoetin β, with strong temporal relationships. *Nephrol Dial Transplant* 2004; **19**: 2133–6.
5. Bennett CL, *et al.* Pure red-cell aplasia and epoetin therapy. *N Engl J Med* 2004; **351**: 1403–8.
6. Gershon SK, *et al.* Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346**: 1584–5.
7. Casadevall N, Mayeux P. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346**: 1585. Correction. *ibid.*; **347**: 458.
8. Macdougall IC. Pure red cell aplasia with anti-erythropoietin antibodies occurs more commonly with one formulation of epoetin alfa than another. *Curr Med Res Opin* 2004; **20**: 83–6.
9. Janssen-Ortho. Important drug safety information: Eprex (epoetin alfa) sterile solution revised prescribing information for patients with chronic renal failure (January 13, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/eprex_3_hpc-cps-eng.pdf (accessed 29/08/08)
10. Rossert J, *et al.* Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol* 2004; **15**: 398–406.
11. Amgen USA. Aranesp (darbepoetin alfa), November 2005. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164147.pdf (accessed 13/08/10)
12. Verhelst D, *et al.* Treatment of erythropoietin-induced pure red cell aplasia: a retrospective study. *Lancet* 2004; **363**: 1768–71.

Effects on electrolytes. Hyperkalaemia and hyperphosphataemia may occur in patients receiving recombinant human erythropoietin. However, hypophosphataemia has also been reported in cirrhotic patients given erythropoietin before autologous blood donation.[1]

1. Kajikawa M, *et al.* Recombinant human erythropoietin and hypophosphatemia in patients with cirrhosis. *Lancet* 1993; **341**: 503–4.

Effects on mental function. Visual hallucinations occurred in 4 patients during treatment with recombinant human erythropoietin, stopped when treatment was withdrawn, and recurred in 2 patients when erythropoietin was reinstituted.[1] Commenting on these and a further 7 cases,[2] the manufacturers considered the reaction to be extremely rare and that the contribution of concurrent medication could not be discounted. In two groups of dialysis patients treated with recombinant human erythropoietin, 15 of 134 and 2 of 103 had visual hallucinations.[3] Increasing age appeared to be a risk factor. Hallucination, associated with hypertension, has occurred during epoetin therapy in a patient with a history of bone marrow transplantation.[4]

1. Steinberg H. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325**: 285.
2. Stead RB. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325**: 285.
3. Steinberg H, *et al.* Erythropoietin and visual hallucinations in patients on dialysis. *Psychosomatics* 1996; **37**: 556–63.
4. van den Bent MJ, *et al.* Erythropoietin induced visual hallucinations after bone marrow transplantation. *J Neurol* 1999; **246**: 614–16.

Effects on the skin. Rashes may occur during treatment with recombinant human erythropoietin.

Pseudoporphyria cutanea tarda, a photosensitivity disorder, has been reported in 2 children undergoing peritoneal dialysis and receiving erythropoietin.[1] However, it was pointed out that this disorder has occurred in adults undergoing dialysis and the children were also receiving other potential photosensitisers.

A fatal case of erythema multiforme has been attributed to a single dose of epoetin alfa. The patient also had eosinophilia and systemic symptoms suggestive of DRESS syndrome.[2]

1. Harvey E, *et al.* Pseudoporphyria cutanea tarda: two case reports on children receiving peritoneal dialysis and erythropoietin therapy. *J Pediatr* 1992; **121**: 749–52.
2. Norgard N, Wall GC. Possible drug rash with eosinophilia and systemic symptoms syndrome after exposure to epoetin alfa. *Am J Health-Syst Pharm* 2005; **62**: 2524–6.

Effects on the spleen. Aggravation of splenomegaly was reported in 2 patients with myeloproliferative disorders after use of recombinant human erythropoietin.[1] Splenic infarction has been reported in a patient with aplastic anaemia given erythropoietin,[2] and peliosis of the spleen was discovered at autopsy in a patient with end-stage renal failure who had been receiving erythropoietin.[3]

1. Iki S, *et al.* Adverse effect of erythropoietin in myeloproliferative disorders. *Lancet* 1991; **337**: 187–8.
2. Imashuku S, *et al.* Splenic infarction after erythropoietin therapy. *Lancet* 1993; **342**: 182–3.
3. Lam KY, *et al.* Peliosis of the spleen: possible association with chronic renal failure and erythropoietin therapy. *Postgrad Med J* 1995; **71**: 493–6.

Effects of subcutaneous injection. Localised pain can occur on subcutaneous injection of human recombinant erythropoietin. In comparisons of preparations it has been suggested that different excipients may affect this.[1-5] It has generally been reported that epoetin alfa preparations containing citrate buffer are more painful than those with phosphate buffer, and that epoetin beta preparations are less painful than epoetin alfa preparations.

1. Frenken LAM, *et al.* Assessment of pain after subcutaneous injection of erythropoietin in patients receiving haemodialysis. *BMJ* 1991; **303**: 288.
2. Lui SP, *et al.* Pain after subcutaneous injection of erythropoietin. *BMJ* 1991; **303**: 856.
3. Yu AW, *et al.* Pain perception following subcutaneous injections of citrate-buffered and phosphate-buffered epoetin alfa. *Int J Artif Organs* 1998; **21**: 341–3.
4. Veys N, *et al.* Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. *Clin Nephrol* 1998; **49**: 41–4.
5. Cumming MN, *et al.* Subcutaneous erythropoietin alpha (Eprex) is more painful than erythropoietin beta (Recormon). *Nephrol Dial Transplant* 1998; **13**: 817.

Treatment of adverse effects. Venesection[1] and erythropheresis[2] have been used to treat raised haematocrit and haemoglobin concentrations caused by recombinant human erythropoietin overdose. Venesection also successfully reduced the blood pressure in 4 patients with life-threatening hypertension associated with recombinant human erythropoietin treatment.[3] None of the patients had a raised haematocrit and the hypertension had been unresponsive to antihypertensive therapy.

1. Brown KR, *et al.* Recombinant erythropoietin overdose. *Am J Emerg Med* 1993; **11**: 619–21.
2. Hoffman RS, *et al.* Erythropoietin overdose treated with emergent erythropheresis. *Vet Hum Toxicol* 2002; **44**: 157–9.
3. Fahal IH, *et al.* Phlebotomy for erythropoietin-associated malignant hypertension. *Lancet* 1991; **337**: 1227.

Precautions

Epoetins should be used with caution in patients with hypertension, a history of seizures, thrombocytosis, chronic hepatic impairment, ischaemic vascular disease, or in patients with malignant tumours. Hypertension should be well controlled before treatment is started and blood pressure monitored during treatment.

Response to epoetins may be diminished by iron deficiency, infection or inflammatory disorders, haemolysis, or aluminium intoxication. Anaemia due to folic acid and vitamin B_{12} deficiencies should also be excluded, since these may also reduce the response. Patients developing sudden lack of efficacy should be investigated. If pure red cell aplasia is diagnosed treatment should be stopped and testing for epoetin antibodies considered; patients should not be transferred to another epoetin.

Patients undergoing dialysis may require increased doses of heparin in view of the increase in packed cell volume.

Platelet counts, haemoglobin concentrations, and serum-potassium concentrations should be monitored regularly.

Dosage must be carefully controlled to avoid too fast an increase in haematocrit and haemoglobin, and recommended values should not be exceeded because of the increased risks of hypertension and thrombotic events.

For reference to the potential effect of epoetins on tumour progression and progression-free survival when used in patients with cancer, see under Anaemias in Uses and Administration, p. 1142.3.

Abuse. The potential dangers from abuse of recombinant human erythropoietin by athletes have been reviewed.[1] Normally, optimal athletic conditioning leads to little change in red cell volume but a significant increase in plasma volume and total blood volume. In contrast, the artificial increase in the red cell mass induced by epoetin is usually accompanied by a decrease in plasma volume and no change in total blood volume. Lack of medical supervision and fluid loss during endurance events increase the risk of serious adverse consequences of these changes in blood viscosity produced by such misuse of epoetin. In one case,[2] cerebral sinus thrombosis in a cyclist was attributed to the combined use of epoetin, human growth hormone, and high doses of vitamins A and E.

1. Spivak JL. Erythropoietin use and abuse: when physiology and pharmacology collide. *Adv Exp Med Biol* 2001; **502**: 207–24.
2. Lage JMM, *et al.* Cyclist's doping associated with cerebral sinus thrombosis. *Neurology* 2002; **58**: 665.

Haematocrit and haemoglobin. A study[1] involving 1233 patients undergoing haemodialysis and suffering from heart failure or ischaemic heart disease found that erythropoietin in doses sufficient to increase haematocrit to 42% (within the normal range) was associated with lack of benefit and a trend towards increased mortality when compared with doses sufficient to maintain a lower haematocrit of around 30%. However, these results are difficult to interpret, since within each group, increased haematocrit was associated with lower mortality, despite the between-group differences. The possibility that intravenous iron supplementation might have contributed to these adverse results was considered, but commentators suggested that until further data were available aiming for a haematocrit of 33 to 36%, and using intravenous iron supplementation where necessary, was still appropriate.[2]

Two studies have looked at the effects of adjusting haemoglobin to different concentrations in patients with chronic renal impairment who did not yet need dialysis. In the CHOIR study[3] of 1432 patients, epoetin alfa was used to adjust haemoglobin to either 11.3 or 13.5 g per 100 mL. The risk of cardiovascular complications, particularly death and hospitalisation for congestive heart failure, was increased in the group with the higher haemoglobin target, without any additional improvement in quality of life. The CREATE study[4] included 603 patients who were treated with epoetin beta to adjust haemoglobin to either 13.0 to 15.0 g per 100 mL or 10.5 to 11.5 g per 100 mL. Although the measures for quality of life were better in the group adjusted to the higher target and there was no statistically significant difference between the groups in the risk of cardiovascular complications, there was a trend towards a more favourable outcome in the low-target group. The FDA subsequently issued a reminder[5] that in patients receiving epoetins or darbepoetin alfa, a target haemoglobin range of 10 to 12 g per 100 mL was recommended, and that haemoglobin concentrations and blood pressure should be monitored. Further information on cardiovascular effects was generated by the placebo-controlled TREAT study[6] of 4038 patients with type 2 diabetes and chronic renal disease, but not needing dialysis, in which darbepoetin alfa was used to target a maintenance haemoglobin of 13.0 g per 100 mL (a median of 12.5 was achieved), compared with about 10.6 g per 100 mL in the placebo group. Although there were no significant differences in death or overall cardiovascular events, stroke was significantly more likely to occur in patients given darbepoetin alfa. A meta-analysis[7] of 27 studies, including these 3, concluded that targeting higher haemoglobin concentrations increased the risk for stroke, hypertension, and vascular access thrombosis, and probably increased the risk for death, serious cardiovascular events, and end-stage renal disease. Subsequent to the TREAT study the FDA[8] amended its recommendations for patients with chronic renal disease: consider starting epoetin or darbepoetin alfa when the haemoglobin level is less than 10 g per 100 mL, use the lowest dose necessary to reduce the need for blood transfusion, and reduce the dose or stop therapy if the haemoglobin exceeds 10 g per 100 mL in patients not on dialysis or when it approaches or exceeds 11 g per 100 mL in patients on dialysis.

1. Besarab A, *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339**: 584–90.
2. Adamson JW, Eschbach JW. Erythropoietin for end-stage renal disease. *N Engl J Med* 1998; **339**: 625–7.
3. Singh AK, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085–98.
4. Drüeke TB, *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355**: 2071–84.
5. FDA. Information for healthcare professionals: erythropoiesis stimulating agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)] (issued 16th November, 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126488.htm (accessed 13/08/10)
6. Pfeffer MA, *et al.* TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361**: 2019–32.
7. Palmer SC, *et al.* Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010; **153**: 23–33.
8. FDA. Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease (issued 24th June, 2011). Available at: http://www.fda.gov/DrugsDrugSafety/ucm259639.htm (accessed 02/08/11)

Resistance. Many factors may contribute to a poor response to recombinant human erythropoietin (see Precautions, above). A study in patients with anaemia of end-stage renal disease[1] found that inadequate dialysis was associated with a reduced response to erythropoietin treatment. The dialysis time and mode of dialysis may also influence response to erythropoietin therapy.[2] Antibodies to recombinant human erythropoietin have also been

reported.[3,4] Delayed clinical response to recombinant human erythropoietin in a patient[5] could have been due to an inherited subclinical pyruvate kinase deficiency.

1. Ifudu O, *et al.* The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 1996; 334: 420–5.
2. Locatelli F, *et al.* The modality of dialysis treatment: does it influence the response to erythropoietin treatment? *Nephrol Dial Transplant* 2001; 16: 1971–4.
3. Peces R, *et al.* Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; 335: 523–4.
4. Viron B, *et al.* Anticorps anti-érythropoiétine humaine recombinante: une cause exceptionnelle de résistance à l'érythropoiétine. *Nephrologie* 2002; 23: 19–22.
5. Zachée P, *et al.* Pyruvate kinase deficiency and delayed clinical response to recombinant human erythropoietin treatment. *Lancet* 1989; i: 1327–8.

Pharmacokinetics

Epoetins show some differences in their pharmacokinetics, possibly due to differences in glycosylation and in the formulation of the commercial preparations.

Epoetin alfa is slowly and incompletely absorbed after subcutaneous injection, and a relative bioavailability of about 10 to 20% has been reported. Peak concentrations after epoetin alfa intravenously are attained within 15 minutes, and within 5 to 24 hours after subcutaneous injection.

The elimination half-life of epoetin alfa after intravenous doses has been reported to be 4 to 13 hours in patients with chronic renal failure; the half-life is generally less in patients with normal renal function. An estimated elimination half-life of about 24 hours has been reported for epoetin alfa given subcutaneously.

Epoetin beta is similarly slowly and incompletely absorbed after subcutaneous injection, and its absolute bioavailability has been reported to be 23 to 42%. Peak serum concentrations are attained within 12 to 28 hours of subcutaneous doses. An elimination half-life of 4 to 12 hours has been reported after intravenous doses and a terminal half-life of 13 to 28 hours after subcutaneous doses.

Epoetin lambda is slowly and incompletely absorbed after subcutaneous injection, with peak serum concentrations occurring between 6 and 24 hours, and a bioavailability of 20 to 30%. After intravenous administration the mean half-life in healthy subjects ranges from 2.5 to 6.7 hours. The estimated half-life following subcutaneous use is 24 hours.

Epoetin theta is slowly and incompletely absorbed after subcutaneous injection, with peak serum concentrations occurring after about 10 to 14 hours and a bioavailability of about 31%. Elimination half-lives of 6 and 4 hours have been reported after single and repeated intravenous doses in patients with chronic renal failure undergoing haemodialysis. Half-lives ranging from 22 to 41 hours have been reported after subcutaneous injection in healthy subjects and other patient groups.

Epoetin zeta has a bioavailability of about 20% after subcutaneous injection, and peak serum concentrations occur after about 12 to 18 hours. The half-life after subcutaneous injection has been estimated to be about 24 hours. After intravenous injection, a half-life of about 4 hours has been measured in healthy subjects, and about 5 hours in patients with chronic renal failure; the half-life in children is about 6 hours.

References.
1. Macdougall IC, *et al.* Clinical pharmacokinetics of epoetin (recombinant human erythropoietin). *Clin Pharmacokinet* 1991; 20: 99–113.
2. Halstenson CE, *et al.* Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 1991; 50: 702–12.
3. Gladziwa U, *et al.* Pharmacokinetics of epoetin (recombinant human erythropoietin) after long term therapy in patients undergoing haemodialysis and haemofiltration. *Clin Pharmacokinet* 1993; 25: 145–53.
4. Montini G, *et al.* Pharmacokinetics and hematologic response to subcutaneous administration of recombinant human erythropoietin in children undergoing long-term peritoneal dialysis: a multicenter study. *J Pediatr* 1993; 122: 297–302.
5. Brown MS, *et al.* Single-dose pharmacokinetics of recombinant human erythropoietin in preterm infants after intravenous and subcutaneous administration. *J Pediatr* 1993; 122: 655–7.
6. Reddingius RE, *et al.* Pharmacokinetics of recombinant human erythropoietin in children treated with continuous ambulatory peritoneal dialysis. *Eur J Pediatr* 1994; 153: 850–4.
7. Chakraborty A, *et al.* Population pharmacokinetics of erythropoietin in critically ill subjects. *J Clin Pharmacol* 2005; 45: 193–202.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Epogen; Eprex; Eritrogen; Hemax; Hypercrit; Pronivel; Recormon; *Austral.*: Eprex; NeoRecormon; Novicrit; *Austria*: Abseamed; Binocrit; Eporatio; Erypo; NeoRecormon; Retacrit; *Belg.*: Binocrit; Eprex; NeoRecormon; *Braz.*: Eprex; Eritina†; Eritromax; Hemax-Eritron; Hemoprex; Ior Epocim; Recormon; Tinax; *Canad.*: Eprex; *Chile*: Epokine; Eprex†; Hepta; Hypercrit; Recormon; *China*: Epiao (益比奥); Espo (利血宝); Espogen (阿司伯根); Hemax (弘能); Huan Er Bo (环尔博); Jia Lin Hao (佳林豪); Jimaixin (济脉欣); Ninghongxin (宁红欣); Nuo Zhi Su (诺之素); Recormon (罗可曼); Sai Bo Er (赛博尔); Xue Da Sheng (雪达升); Yi Bei (依倍); Yi Pu Ding (依普定); Yi Pu Li (怡普利); Yibao (怡宝); *Cz.*: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; *Denm.*: Eprex; NeoRecormon; Retacrit; *Fin.*: Eprex; NeoRecormon; *Fr.*: Binocrit; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; *Ger.*: Abseamed; Binocrit†; Biopoin; Dynepo†; Eporatio; Erypo; NeoRecormon; Retacrit; Silapo; *Gr.*: Abseamed; Binocrit; Dynepo; Eprex; NeoRecormon; Recormon; Retacrit; *Hong Kong*: Eprex; Recormon; *Hung.*: Binocrit; Eporatio; Eprex; NeoRecormon; Retacrit; *India*: Cerition; Epofer; Eponis 2K; Eposis; Epotin; Epotop; Epox; Eprex; Erypro; Espogen; Hemax; LG Espogen; NeoRecormon; Wepox; *Indon.*: Epoglobin; Epotrex-NP; Eprex; Hemapo; Recormon; *Irl.*: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; *Israel*: Binocrit; Eporatio; Eprex; Recormon; *Ital.*: Abseamed; Binocrit; Dynepo†; Eprex; NeoRecormon; Retacrit; *Jpn*: Epogin; Espo; *Malaysia*: Eprex; Recormon; *Mex.*: Alveritin; Bioyetin; Epomax; Eprex; Erlan; Exetin-A; Hypercrit†; Negortire; Recormon; Yepotin†; *Neth.*: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; *Norw.*: Eprex; NeoRecormon; Retacrit; *NZ*: Eprex; NeoRecormon; Recormon†; *Philipp.*: Efotin; Epogen; Epokine; Eposino; Epotin; Eprex; Recormon; Renogen; Shanpoietin; Wepox; *Pol.*: Abseamed; Binocrit; Biopoin; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; *Port.*: Abseamed; Binocrit; Biopoin; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; Silapo; *Rus.*: Epocomb (Эпокомб); Epocrin (Эпокрин); Epostim (Эпостим); Eprex (Эпрекс); Eralfon (Эральфон); Erythrostim (Эритростим); Recormon (Рекормон); *S.Afr.*: Eprex; Recormon; Repotin; *Singapore*: Eprex; Recormon; *Spain*: Binocrit; Dynepo†; Epopen†; Eporatio; Eprex; NeoRecormon; Retacrit; *Swed.*: Binocrit; Eporatio; Eprex; NeoRecormon; Retacrit; *Switz.*: Abseamed; Binocrit; EpoTheta; Eprex; Recormon; *Thai.*: EPIAO; Epokine; EPOO†; Eporon†; Eposis; Eprex; Eritine; Eritrogen; Espogen; Hemapo; Hemax; Recormon; Renogen; *Turk.*: Epobel; Eprex; NeoRecormon; Recormon; *UAE*: Epotin; *UK*: Binocrit; Dynepo†; Eporatio; Eprex; NeoRecormon; Retacrit; *Ukr.*: Epobiokrin (Эпобиокрин); Epovitan (Эповитан); Erythroetin (Эритроэтин); Recormon (Рекормон); Wepox (Вепокс)†; *USA*: Epogen; Procrit; *Venez.*: Eprex; Hypercrit; Recormon.

Pharmacopoeial Preparations
BP 2014: Erythropoietin Injection.

Etamsylate *(BAN, rINN)*

Ciclonamina; Cyclonamine; E-141; Etamsilat; Etamsilatas; Etamsilato; Etamsylaatti; Etamsylat; Etamsylát; Étamsylate; Etamsylatum; Etamszilát; Ethamsylate (USAN); Ethamsylate; MD-141; Этамзилат.

Diethylammonium 2,5-dihydroxybenzenesulphonate.

$C_{10}H_{17}NO_5S$=263.3

CAS — 2624-44-4.

ATC — B02BX01.

ATC Vet — QB02BX01.

UNII — 24YL531VOH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Etamsylate). A white or almost white, crystalline powder. It shows polymorphism. Very soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 10% solution in water has a pH of 4.5 to 5.6. Store in airtight containers. Protect from light.

Uses and Administration

Etamsylate is a haemostatic that appears to maintain the stability of the capillary wall and correct abnormal platelet adhesion. It is given for the prophylaxis and control of haemorrhages from small blood vessels.

For short-term treatment of blood loss in menorrhagia (below) a dose of 500 mg is given orally four times daily during menstruation. For the control of haemorrhage after surgery etamsylate may be given orally or by intramuscular or intravenous injection in a dose of 250 to 500 mg. A dose may be given 1 hour before surgery, and further doses given after surgery and repeated every 4 to 6 hours as necessary. Intravenous doses may be given during surgery if necessary. For etamsylate use in prophylaxis of neonatal intraventricular haemorrhage, see below.

Administration in children. For information on etamsylate prophylaxis of intraventricular haemorrhage in premature neonates, see below.

Menorrhagia. When given during menstruation to women with idiopathic menorrhagia (p. 2300.3), etamsylate was as effective as mefenamic acid in reducing uterine blood loss in 1 study,[1] but was ineffective in another.[2] A review, which included published and unpublished results from these and 2 earlier studies, reported that etamsylate produced about a 10 to 15% reduction in menstrual blood loss.[3] Etamsylate is now considered to be less effective than other treatments for menorrhagia, and is no longer recommended.[4]

1. Chamberlain G, *et al.* A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. *Br J Obstet Gynaecol* 1991; 98: 707–11.
2. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; 313: 579–82.
3. Coulter A, *et al.* Treating menorrhagia in primary care: an overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care* 1995; 11: 456–71.
4. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 06/03/08)

Neonatal intraventricular haemorrhage. Etamsylate is one of several drugs that have been tried in the prevention of intraventricular haemorrhage in very low birthweight infants (p. 1128.3). In some countries it is licensed for intramuscular use in doses of 10 mg/kg. The first dose is given within the first 2 hours after birth, and repeated every 6 hours for 4 days.

Some studies have used mainly the intravenous route. In a multicentre, placebo-controlled, double-blind study,[1] etamsylate was given in an initial dose of 12.5 mg/kg intravenously or intramuscularly within 1 hour of delivery, followed by the same dose intravenously every 6 hours for 4 days to a total dose of 200 mg/kg. Of 330 infants who had had no evidence of haemorrhage soon after delivery, the subsequent incidence of haemorrhage in the 162 who received etamsylate was reduced, particularly the more extensive grades when compared with the 168 who received placebo. Of a further 30 infants with evidence of periventricular haemorrhage before treatment, 21 were given etamsylate and 9 placebo; treatment with etamsylate limited the extension of bleeding. There was also a reduction in patent ductus arteriosus in the treated infants. However, a subsequent study using the same dosage regimen,[2] showed little benefit on short-term follow-up. It was considered that the study size may have been too small and the drug given too late; the initial dose was given within 4 hours of birth whereas, in the previous study, treatment was started within 1 hour of birth. Follow-up[3] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Developmental outcome assessments at about 4 years of age in patients from the first study[4] also found that despite the original reduction in intraventricular haemorrhage with etamsylate, it had not reduced cerebral palsy compared with the control group.

1. Benson JWT, *et al.* Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet* 1986; ii: 1297–1300.
2. The EC Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates: early mortality and morbidity. *Arch Dis Child* 1994; 70: F201–F205.
3. Elbourne D, *et al.* Randomised controlled trial of prophylactic etamsylate: follow up at 2 years of age. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F183–F187.
4. Schulte J, *et al.* Developmental outcome of the use of etamsylate for prevention of periventricular haemorrhage in a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F31–F35.

Adverse Effects and Precautions

Nausea, vomiting, diarrhoea, fever, headache, and rashes have occurred after use of etamsylate. Headache and rashes may disappear on reduced dosage, and gastrointestinal disturbances are reduced by giving etamsylate after food. Transient hypotension has been reported after intravenous injection.

Pharmacokinetics

Etamsylate is absorbed from the gastrointestinal tract. It is excreted unchanged, mainly in the urine. Etamsylate is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Impedil; *Belg.*: Dicynone; *Braz.*: Dicinone; *Chile*: Dicynone; *China*: Ai Fen (艾分); An Di Xin (安迪欣); Heng Zhi (恒智); Ka Le (卡乐); Lizhining (力制凝); Ni Ji (尼基); Tian Yi Shu (天亦舒); Xun Di (迅迪); Zhuo Xun (卓迅); *Cz.*: Dicynone; *Fr.*: Dicynone; *Hung.*: Dicynone; *India*: Alstat; Amilate; Bloc; Botrostat; C-Sylate; Capilyte; Clotawin; Cosklot; Cotham; Culoc; Dicynene; Disylate; Eith; Eklot; Elyte; Emsulate; Ensulate; Eselin; Ethacid; Ethafy; Ethaklot; Ethamclp; Ethams; Ethamstat; Ethariv; Ethasyl; Etholate; Ethver; Ethylate; Eustal; Floban; H-Stat; Hamodam; Hemklot; Hemoclot; Hemolate; Hemostat; Hemsyl; Himolan; Kelate; Kloty; Late; Masyla; Mazo; Medistat; Noflo; Revici-E; *Indon.*: Dicynone; *Irl.*: Dicynene; *Ital.*: Dicynone; Eselin; *Mex.*: Dicynone; *Rus.*: Dicynone (Дицинон); *Singapore*: Dicynone; *Spain*: Dicinone†; Hemo 141; *Switz.*: Dicynone; *UK*: Dicynene; *Ukr.*: Dicynone (Дицинон); *Venez.*: Dicynone.

Multi-ingredient Preparations. *India*: C-Sylate Plus; Capihem; Capitrax Plus; Clotawin-T; Clotem Plus; Coag; Coastat Plus; Cosklot Plus; Eklot-MF; Etam; Etex-T; Ethatol; ETM-T; Etosys;

Fetran-ES; Fibran Plus; Hamodam-T; Hemocrat; Klotinex; Menoguard; Menostat; No Blos For.

Etherified Starches ⊗

Almidon, éteres de; HES; Hydroxyethyl Starch; Hydroxyéthylamidon; Hydroxyethylamylum.

2-Hydroxyethyl ether starch.

CAS — 9005-27-0.
ATC — B05AA07.
ATC Vet — QB05AA07.
UNII — 875Y4127EA (hetastarch).

Description. Etherified starches are starches that are composed of more than 90% of amylopectin and that have been etherified to varying extents.

- hetastarch (*BAN, USAN*): an average of 7 or 8 of the hydroxy groups in each 10 D-glucopyranose units of starch polymer have been converted into OCH_2CH_2OH groups
- hydroxyethyl starch 130/0.4 (*USAN*): an average of 3.8 to 4.5 of the hydroxy groups in each 10 D-glucopyranose units of starch polymer have been converted into OCH_2CH_2OH groups
- pentastarch (*BAN, USAN*): an average of 4 or 5 of the hydroxy groups in each 10 D-glucopyranose units of the starch polymer have been converted to OCH_2CH_2OH groups

Etherified starches also vary in terms of average molecular weight and the position of etherification within the glucopyranose unit.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Starches, Hydroxyethyl; Amyla Hydroxyethyla). Hydroxyethyl starches are partially substituted poly(2-hydroxyethyl)ethers of waxy maize starch or potato starch, which primarily consist of amylopectin. The type of hydroxyethyl starch is defined by 2 numbers: the mean molecular weight and the number of hydroxyethyl groups per anhydroglucose unit expressed as the molar substitution. Hydroxyethyl starch is also characterised by the number of hydroxyethyl groups located at the C2 group over the number of hydroxyethyl groups located at C6, expressed as the C2/C6 ratio. White or almost white powders. Hygroscopic until a water content of about 12 to 15% is reached. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in anhydrous ethanol.

Incompatibility. Hetastarch is incompatible with many compounds including some injectable antibacterials.

References.
1. Wohlford JG, Fowler MD. Visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1989; 46: 995–6.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; 47: 297–8.

Uses and Administration

Etherified starches are plasma volume expanders used in the management of hypovolaemic shock (p. 1279.3). Those most commonly used include high-molecular-weight hetastarch (weight average molecular weight 450 000 to 480 000) and medium-molecular-weight pentastarch (weight average molecular weight 200 000 to 250 000). Other etherified starches that are used include low-molecular-weight tetrastarch (hydroxyethyl starch 130/0.4), low-molecular-weight pentastarch, and medium-molecular-weight hexastarch, which has a degree of etherification between that of pentastarch and hetastarch. A higher molecular weight hetastarch is also available. Isooncotic solutions of etherified starches, for example, 6% hetastarch or 6% medium-molecular-weight pentastarch, exert a similar colloidal osmotic pressure to human albumin, and when given by intravenous infusion produce an expansion of plasma volume slightly in excess of the infused volume. Hyperoncotic solutions, for example 10% medium-molecular-weight pentastarch, produce an expansion of plasma volume of about 1.5 times the infused volume. The duration of effect depends on the characteristics of the starch used; for 6% hetastarch the effect lasts for 24 to 36 hours.

Etherified starches are given intravenously as solutions in sodium chloride 0.9% or other electrolytes; concentrations used are usually 6 or 10%, although 3% solutions are also available for some. The dose and rate of infusion depend on the amount of fluid lost and degree of haemoconcentration; usual doses are in the range of 500 to 2500 mL daily, depending on the preparation used, and the infusion rate may be up to about 20 mL/kg per hour if necessary.

Hetastarch and pentastarch increase the erythrocyte sedimentation rate when added to whole blood. They are therefore used in leucapheresis procedures to increase the yield of granulocytes. Doses of 250 to 700 mL may be added to venous blood in the ratio 1 part to at least 8 parts of whole blood in such procedures. Up to 2 such procedures per week and a total of 7 to 10 have been reported to be safe.

Hetastarch and hexastarch have also been used in extracorporeal perfusion fluids.

References.
1. Treib J, *et al.* An international view of hydroxyethyl starches. *Intensive Care Med* 1999; 25: 258–68.

Administration in children. Etherified starches of various degrees of substitution and molecular weights have been used as plasma expanders in children.[1-3]

1. Brutocao D, *et al.* Comparison of hetastarch with albumin for postoperative volume expansion in children after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1996; 10: 348–51.
2. Paul M, *et al.* A randomized, controlled study of fluid management in infants and toddlers during surgery: hydroxyethyl starch 6% (HES 70/0.5) vs lactated Ringer's solution. *Paediatr Anaesth* 2003; 13: 603–8.
3. Liet J-M, *et al.* Plasma volume expansion by medium molecular weight hydroxyethyl starch in neonates: a pilot study. *Pediatr Crit Care Med* 2003; 4: 305–7.

Stroke. Haemodilution with pentastarch has been tried in patients with acute ischaemic stroke (p. 1269.2) in an attempt to improve reperfusion of the brain by lowering blood viscosity. However, one study was terminated early when an excess mortality was noted in the haemodilution group.[1] The early fatalities occurred almost exclusively in patients with severe strokes; cerebral oedema was the main cause of death within one week of the onset of symptoms. Among the survivors neurological recovery was better among those who received haemodilution. A systematic review[2] of 18 haemodilution studies, which included 5 using etherified starches, found no benefit in terms of fatality or functional outcome with haemodilution. See also Effects on the Blood, below

1. Hemodilution in Stroke Study Group. Hypervolemic hemodilution treatment of stroke: results of a randomized multicenter trial using pentastarch. *Stroke* 1989; 20: 317–23.
2. Asplund K. Haemodilution for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 27/10/05).

Adverse Effects and Precautions

Hypersensitivity reactions including anaphylactic reactions have occurred after infusion of etherified starches. Pruritus can occur after long-term use of high doses of etherified starches; the onset may be delayed until weeks after the last infusion. Serum-amylase concentrations may appear to increase during infusion of etherified starches due to formation of an enzyme-substrate complex that is only eliminated slowly.

Precautions that should be observed with plasma expanders are described under Dextran 70, p. 1139.2, and these should be considered when etherified starches are used. There may be some interference with blood grouping and cross-matching of blood.

Reviews.
1. Wiedermann CJ. Hydroxyethyl starch - can the safety problems be ignored? *Wien Klin Wochenschr* 2004; 116: 583–94.

Effects on the blood. Use of plasma expanders causes dilution of clotting factors and may also have direct effects on coagulation. Effects of etherified starches on the coagulation system include[1,2] a decrease in clotting factor VIII and von Willebrand factor that results in an acquired type I von Willebrand disease (see p. 1129.3), a prolongation of the activated partial thromboplastin time, and a reduction in platelet volume. The extent of these effects appears to depend on the molecular weight and the rate of degradation *in vivo* of the starch. Etherified starches of high molecular weight that are more slowly degraded (due to a high degree of substitution or a high ratio of hydroxyethylation at the C2:C6 positions) have a greater effect on blood coagulation than medium and low molecular weight, easily degraded, etherified starches. Coagulopathy and haemorrhage have been reported with the use of solutions of etherified starches.[1,3] Serious complications such as intracranial bleeding and cerebral oedema have been reported in studies of patients with ischaemic stroke and other brain injuries who have been treated with etherified starches of various molecular weights and degrees of substitution, and several studies have been stopped prematurely as a result.[4]

1. Treib J, *et al.* Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; 78: 974–83.
2. de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; 29: 1261–7.
3. Jonville-Béra A-P, *et al.* Acquired type I von Willebrand's disease associated with highly substituted hydroxyethyl starch. *N Engl J Med* 2001; 345: 622–3.
4. Wiedermann CJ. Complications of hydroxyethyl starch in acute ischemic stroke and other brain injuries. *Pathophysiol Haemost Thromb* 2003; 33: 225–8.

Effects on the kidneys. Osmotic-nephrosis-like lesions found at biopsy in some transplanted kidneys have been attributed to use of solutions of etherified starches in the donor patient.[1] Such use has also been reported to impair immediate graft function.[2] However, another study[3] found no association between the use of these solutions in the donor patient and osmotic-nephrosis-like lesions or delayed graft function. Oliguric acute renal failure and osmotic-nephrosis-like lesions occurred in a patient who was given an etherified starch infusion during surgery for carcinoma of the tonsils.[4]

Etherified starches should be used with caution in patients with renal impairment.

1. Legendre CH, *et al.* Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; 342: 248–9.
2. Cittanova ML, *et al.* Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; 348: 1620–22.
3. Coronel B, *et al.* Hydroxyethylstarch and renal function in kidney transplant recipients. *Lancet* 1997; 349: 884.
4. De Labarthe A, *et al.* Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient. *Am J Med* 2001; 111: 417–18.

Effects on the skin. Pruritus has been reported after infusion of etherified starches.[1] It appears to be associated with tissue deposition of the starch although the actual mechanism by which this provokes pruritus is unresolved. The effect appears to be dose-related, which may explain the differences in reported incidences that have ranged from less than 10% to more than 60% of patients being affected. The molecular weight and degree of substitution of the etherified starch do not appear to be risk factors. The pruritus is usually generalised, but there are reports of localised pruritus affecting the trunk, extremities, anogenital area, and head and neck. It is frequently severe, persistent, and refractory to treatment, causing sleep disturbances and adversely affecting quality of life. Attacks of pruritus may be precipitated by heat, sweating, exercise, bathing, mechanical pressure, and mental stress. It typically has a delayed onset of 1 to 6 weeks after exposure to the etherified starch. Average durations of 9 to 15 weeks have been reported, but in some cases pruritus has continued for up to 2 years. The condition is generally unresponsive to treatment, although there have been reports of relief with topical capsaicin, ultraviolet therapy, or oral naltrexone.

Marked and persistent periocular swelling developed in a patient after 15 daily infusions of hetastarch.[2] Abnormal accumulation of hetastarch was found in the periocular tissues.

1. Bork K. Pruritus precipitated by hydroxyethyl starch: a review. *Br J Dermatol* 2005; 152: 3–12.
2. Kiehl P, *et al.* Decreased activity of acid α-glucosidase in a patient with persistent periocular swelling after infusions of hydroxyethyl starch. *Br J Dermatol* 1998; 138: 672–77.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etherified starches (hydroxyethylstarch) as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

Etherified starches consist of mixtures of molecules with a range of molecular weights and with varying degrees of etherification. After intravenous infusion the molecules with a molecular weight of less than 50 000 are readily excreted unchanged by the kidney; larger molecules are metabolised and eliminated more slowly. The rate of metabolism depends upon the size of the molecule and the degree and position of etherification, with a high molecular weight, high degree of etherification, and etherification mainly at the C2 position leading to a slower rate of metabolism and hence a longer duration of action. About 33% of a dose of high-molecular-weight hetastarch (weight average molecular weight 450 000) and about 70% of a dose of medium-molecular-weight pentastarch (weight average molecular weight 250 000) is excreted in the urine in 24 hours. Etherified starches may be distributed to various tissues; a small proportion of the dose may persist in the body for several years.

References.
1. Mishler JM, *et al.* Changes in the molecular composition of circulating hydroxyethyl starch following consecutive daily infusions in man. *Br J Clin Pharmacol* 1979; 7: 505–9.
2. Mishler JM, *et al.* Post-transfusion survival of hydroxyethyl starch 450/0.70 in man: a long-term study. *J Clin Pathol* 1980; 33: 155–9.
3. Yacobi A, *et al.* Pharmacokinetics of hydroxyethyl starch in normal subjects. *J Clin Pharmacol* 1982; 22: 206–12.
4. Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinet* 2005; 44: 681–99.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hemohes; Hessico; Infukoll HES; Loriness; Venofundin; Voluven; *Austral.*: Voluven; *Austria*: HAES-steril; Hemohes†; HyperHAES; PlasmaHES; Tetraspan; Venofundin; Volulyte; Voluven; *Belg.*: Venohes; *Canad.*: Hextend; Pentaspan; Volulyte; Voluven; *Chile*: HAES-steril; Hemohes; Voluven; *China*: HAES-steril (贺斯); Hemohes (海

斯); Huo Mu (霍姆); HyperHAES (贺苏); Venofundin (文诺方汀); Voluven (万汶); Ying Yuan (盈源); *Cz.*: HAES-steril; Hemohes†; HyperHAES; Plasma Volume; Serag-HAES†; Tetraspan; Volulyte; Voluven; *Denm.*: HAES-steril; Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; *Fin.*: HAES-steril†; Hemohes†; Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; *Fr.*: Heafusine; Hyperhes; PlasmaVolume; Plasmohes; Restorvol; Voluven; *Ger.*: HAES-Rheopond†; HAES-steril; Hemohes; HyperHAES; Infukoll HES; PlasmaVolume; Rheohes†; Serag-HAES†; Tetraspan; Venofundin; Vitafusal; VitaHES; Volulyte; Voluven; *Gr.*: HAES-steril; Hemohes; Hespan; PlasmaVolume; Tetraspan; Venofundin; Volulyte; Voluven; *Hong Kong*: Tetraspan; Volulyte; Voluven; *Hung.*: HAES-steril; Hesra; HyperHAES; Tetraspan; Volulyte; Voluven; *India*: Expan; HAES-steril; Hestar; *Indon.*: Expafusin; Fima HES; HAES-steril; Hemohes†; TetraHES; Voluven; WIDAHES; *Irl.*: HyperHAES; Plasma Volume; Venofundin†; Volulyte; *Israel*: HAES-sterile; Hemohes; Voluven; *Ital.*: Amidolite; HAES-steril; HyperHAES; PlasmaVolume; Tetraspan; Volulyte; Voluven; *Jpn*: Hespander; *Malaysia*: Voluven; *Mex.*: HAES-steril; Hestar; Voluven; *Neth.*: Elohaes; HAES-steril†; Hemohes†; HyperHAES; PlasmaVolume; Tetraspan; Venofundin; Volulyte; Voluven; *Norw.*: Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; *NZ*: Hemohes†; Venofundin; Voluven; *Philipp.*: HAES-steril; Volulyte; Voluven; Xpand; *Pol.*: HAES-steril; Hemohes; HyperHAES; Tetraspan; Volulyte; Voluven; *Port.*: HAES-steril; Hemohes†; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; *Rus.*: HAES-steril (ХАЕС-стерил); Hemohes (Гемохес); HyperHAES (ГиперХАЕС); Infukoll HES (Инфукол ГЭК); Plasmaline (Плазмалин); PolyHES (ПолиХЭС); Refortan (Рефортан); ReoHES (РеоХЕС); Stabisol (Стабизол); Tetraspan (Тетраспан); Volecam (Волекам); Volemcor (Волемкор); Voluven (Волювен); *S.Afr.*: HAES-steril; Venofundin; Vitahes; Voluven; *Singapore*: HAES-steril†; Hemohes; Volulyte; Voluven; *Spain*: Hemohes; Hes Grifols†; PlasmaVolume; Volulyte; Voluven; *Swed.*: HAES-steril†; Hesra; HyperHAES; Tetraspan; Venofundin; Volulyte; Voluven; *Switz.*: HAES-steril; Hemohes†; HyperHAES; Tetraspan; Venofundin; Voluven; *Thai.*: HAES-steril†; Hemohes; Hestar†; TetraHes; Tetraspan; Volulyte; Voluven; *Turk.*: Biohes; Bioplazma†; Expahes; HAES-steril; Hemohes†; HyperHAES; Isohes; Plasmasteril†; Varihes; Voluven; *UK*: HAES-steril†; Hemohes†; HyperHAES†; Infukoll†; Tetraspan†; Venofundin†; Volulyte†; Voluven†; *Ukr.*: Gecodes (Гекодез); Haecodes (Гекодез); HAES-steril (Хаес-Стерил); Hetasorb (Хетасорб); HyperHAES (ГиперХАЕС); Refortan (Рефортан); Stabizol (Стабизол); Venofundin (Венофундин); Voluven (Волювен); *USA*: Hespan; Pentaspan; Voluven.

Multi-ingredient Preparations. *Belg.*: Tetraspan; *Irl.*: EquiHes; Voluven; *Spain*: Isohes; *Thai.*: Infukoll HES†.

Factor VII

Facteur VII; Factor estable; Proconvertin; Proconvertina; SPCA; Stable Factor; Фактор VII.

ATC — B02BD05.

ATC Vet — QB02BD05.

UNII — 4156XVB4QD (human factor VII); 15FH07392N (human factor VIIa).

Description. Factor VII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Eptacog Alfa (Activated) is in use for a recombinant factor VIIa.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Coagulation Factor VII; Factor VII Coagulationis Humanus; Dried Factor VII Fraction BP 2014). A sterile, liquid or freeze-dried preparation of a plasma protein fraction that contains the single-chain glycoprotein factor VII and may also contain small amounts of the activated form, the two-chain derivative factor VIIa, as well as coagulation factors II, IX, and X, and protein C and protein S. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VII fraction is dissolved in a suitable liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. No antimicrobial preservative or antibiotic is added. The specific activity is not less than 2 international units of factor VII per mg of protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 15 international units/mL.

A white or almost white, pale yellow, green, or blue hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Eptacog Alfa (Activated) *(BAN, rINN)*

Eptacog alfa (activado); Eptacog Alfa (activé); Eptacogum Alfa (activatum); Эптаког Альфа (Активированный).

Blood-coagulation factor VII (human clone λHVII2463 protein moiety).

CAS — 102786-52-7; 102786-61-8.

ATC — B02BD08.

ATC Vet — QB02BD08.

UNII — AC71R787OV.

Units

The potency of factor VII is expressed in international units and preparations may be assayed using the International Standard for blood coagulation factor VII concentrate, human (1998).

The potency of factor VIIa (activated factor VII) is expressed in international units and preparations may be assayed using the first International Standard for blood coagulation factor VIIa concentrate (1993).

Uses and Administration

Factor VII may be used as replacement therapy in patients with rare genetic deficiencies of factor VII.

Factor VIIa (activated factor VII) is used to treat bleeding episodes and to prevent bleeding associated with surgery in patients with haemophilia A or haemophilia B who have developed antibodies to factor VIII or factor IX, respectively, and in acquired haemophilia (see Haemophilias, p. 1126.3). It may also be used in congenital factor VII deficiency and Glanzmann's thrombasthenia (see Inherited Haemorrhagic Disorders, p. 1128.2). Factor VIIa may also be useful in patients with von Willebrand's disease (p. 1129.3). Factor VIIa is given as the recombinant form, eptacog alfa (activated). Eptacog alfa (activated) 100 micrograms is equivalent to 5000 international units.

In the treatment of bleeding episodes in patients with **haemophilia**, an initial dose of eptacog alfa (activated) 90 micrograms/kg is given by intravenous bolus injection over 2 to 5 minutes. Further doses may be given as required to achieve and maintain haemostasis, initially every 2 to 3 hours. The dose may then be adjusted (effective doses have ranged from 35 to 120 micrograms/kg), or the dosing interval increased, according to response. Treatment may need to be continued for up to 3 weeks or more following serious bleeding episodes. A similar regimen may be used in patients with haemophilia when they undergo an invasive procedure or surgery, in which case the initial dose should be given immediately before the intervention. Mild to moderate episodes of joint, muscle, or mucocutaneous bleeding may be adequately managed with 2 or 3 doses of 90 micrograms/kg given at 3-hour intervals, with 1 additional dose if required; alternatively, a single dose of 270 micrograms/kg may be given. When these regimens for mild to moderate bleeding are used as home therapy, treatment should not exceed 24 hours.

In **factor VII deficiency**, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 15 to 30 micrograms/kg every 4 to 6 hours until haemostasis is achieved.

In **Glanzmann's thrombasthenia** that is refractory to platelet transfusions, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 90 micrograms/kg every 2 hours; at least 3 doses should be given.

Eptacog alfa pegol (activated), a long-acting pegylated form of the drug, is under investigation in patients with haemophilias A and B who have developed antibodies.

Reviews.

1. Poon M-C. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol* 2001; 8: 312–18.
2. Mladhada MV, *et al.* Recombinant factor VIIa in the treatment of bleeding. *Am J Clin Pathol* 2004; 121: 124–37.
3. Anonymous. Novoseven for non-hemophilia hemostasis. *Med Lett Drugs Ther* 2004; 46: 33–4.
4. Parameswaran R, *et al.* Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; 11: 100–106.
5. Siddiqui MAA, Scott LJ. Recombinant factor VIIa (eptacog alfa): a review of its use in congenital or acquired haemophilia and other congenital bleeding disorders. *Drugs* 2005; 65: 1161–77.
6. Mariani G, *et al.* Congenital factor VII deficiency: therapy with recombinant activated factor VII—a critical appraisal. *Haemophilia* 2006; 12: 19–27.
7. Sumner MJ, *et al.* Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. *Haemophilia* 2007; 13: 451–61.
8. Obergfell A, *et al.* Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature. *Haemophilia* 2008; 14: 233–41.

Administration. Recombinant factor VIIa is usually given by bolus intravenous injection. The successful use of continuous infusion has been described in a few small studies and case reports.[1]

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; 36: 882–91.

Administration in children. Children are generally given similar microgram/kg doses of eptacog alfa (activated) to those used in adults for bleeding in haemophilia (see above). However, children clear the drug faster than adults and may need higher doses to achieve similar plasma concentrations.

The use of eptacog alfa (activated) in children for bleeding of various causes has been reviewed.[1,2]

1. Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders–a 2006 review. *Haemophilia* 2006; 12: 457–72.
2. Goldstein B, *et al.* Evidence-based use of recombinant FVIIa (NovoSeven, NiaStase) for the treatment of hemophilia with inhibitors in children and adolescents. *Transfus Apher Sci* 2008; 38: 25–32.

Haemorrhagic disorders. As well as being used in patients with haemophilia, recombinant factor VIIa has been tried or investigated in patients with bleeding of various other causes.[1,2] There have been reports of recombinant factor VIIa used to manage or prevent bleeding associated with oral[3-5] or parenteral[6] anticoagulants. There are also a few reports of it successfully controlling bleeding associated with diffuse alveolar haemorrhage[7-9] or dengue haemorrhagic fever;[10] it has also been studied in the management of acute variceal bleeding (p. 2563.1). In the management of massive postpartum haemorrhage (p. 2130.2), recombinant factor VIIa is increasingly being used when standard medical and surgical therapies are inadequate. There are suggestions that it may reduce the need for blood products, control bleeding sufficiently to allow transfer of the patient to a facility where angiography and embolisation can be performed, and reduce the need for hysterectomy.[11] However, evidence consists largely of case reports and case series. Although advice has been published, based on this evidence and expert opinion,[12] the place of recombinant factor VIIa in the treatment of postpartum haemorrhage remains to be confirmed. Initial investigation of recombinant factor VIIa in the acute management of intracerebral haemorrhage was promising,[13] but a phase 3 study found that it did not reduce the rates of death or severe disability, compared with placebo.[14] Recombinant factor VIIa is also under investigation in the management of serious bleeding after surgery or trauma.[15,16]

1. Lam MSH, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. *Ann Pharmacother* 2005; 39: 885–91.
2. Mallarkey G, *et al.* An evaluation of eptacog alfa in nonhaemophiliac conditions. *Drugs* 2008; 68: 1665–89.
3. Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002; 137: 884–8.
4. Freeman WD, *et al.* Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clin Proc* 2004; 79: 1495–1500.
5. Talkad A, *et al.* Reversal of warfarin-induced anticoagulation with factor VIIa prior to rt-PA in acute stroke. *Neurology* 2005; 64: 1480–1.
6. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; 44: 718–26.
7. Betensley AD, Yankaskas JR. Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. *Am J Respir Crit Care Med* 2002; 166: 1291–2.
8. Pastores SM, *et al.* Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. *Chest* 2003; 124: 2400–2403.
9. Henke D, *et al.* Successful treatment of diffuse alveolar hemorrhage with activated factor VII. *Ann Intern Med* 2004; 140: 493–4.
10. Chuansumrit A, *et al.* The use of recombinant activated factor VII for controlling life-threatening bleeding in dengue shock syndrome. *Blood Coag Fibrinol* 2004; 15: 335–42.
11. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. *Int J Obstet Anesth* 2007; 16: 29–34.
12. Welsh A, *et al.* Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. *Aust N Z J Obstet Gynaecol* 2008; 48: 12–16.
13. Mayer SA, *et al.* Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; 352: 777–85.
14. Mayer SA, *et al.* FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; 358: 2127–37.
15. Dutton RP, *et al.* Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; 57: 709–18.
16. Levi M, *et al.* Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med* 2005; 33: 883–90.

Adverse Effects and Precautions

Use of eptacog alfa (activated) may be associated with nausea, vomiting, skin reactions, fever, headache, and changes in blood pressure. Reports of hypersensitivity including anaphylaxis are rare, but eptacog alfa (activated) should be avoided or used with caution in patients who are known to be hypersensitive to *mouse*, *hamster*, or *bovine* proteins. Eptacog alfa (activated) should be used with caution in patients with conditions associated with circulating tissue factor, such as advanced atherosclerosis, crush injury, or septicaemia, since there is a risk of precipitating thrombosis or disseminated intravascular coagulation.

Effects on the cardiovascular system. Reports of 185 serious thromboembolic events associated with eptacog alfa (activated), that had been received by the FDA up to the end of 2004, have been reviewed.[1] Data were collected from both clinical studies and spontaneous reports. Various forms of arterial and venous thrombosis had been described, and most events were found to have occurred after its use for unlicensed indications in patients without haemophilia. Thromboembolism in haemophiliacs treated with eptacog alfa (activated) between May 2003 and December 2006 has also been reviewed.[2] The average risk of a thromboembolic event was about 3.75 per 100 000 infusions.

1. O'Connell KA, *et al.* Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; 295: 293–8.
2. Abshire T, Kenet G. Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors. *Haemophilia* 2008; 14: 898–902.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eptacog alfa as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Eptacog alfa (activated) should not be used with activated or nonactivated prothrombin complex concentrates because of an increased risk of thromboembolism.

Pharmacokinetics

The mean terminal half-life of eptacog alfa (activated) is about 3 hours. However, clearance appears to be related to age, and may be increased by more than 50% in children.

References.

1. Klitgaard T, Nielsen TG. Overview of the human pharmacokinetics of recombinant activated factor VII. *Br J Clin Pharmacol* 2008; 65: 3–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: NovoSeven; ***Austral.***: NovoSeven; ***Austria***: NovoSeven; ***Belg.***: NovoSeven; ***Braz.***: NovoSeven; ***Canad.***: NiaStase; ***Chile***: NovoSeven; ***China***: NovoSeven (诺其); ***Cz.***: NovoSeven; ***Denm.***: NovoSeven; ***Fin.***: NovoSeven; ***Fr.***: NovoSeven; ***Ger.***: Immuseven; NovoSeven; ***Gr.***: NovoSeven; ***Hong Kong***: NovoSeven; ***Hung.***: NovoSeven; ***India***: NovoSeven; ***Irl.***: NovoSeven; ***Israel***: NovoSeven; ***Ital.***: NovoSeven; Provertin-UM TIM 3; ***Jpn***: NovoSeven; ***Malaysia***: NovoSeven; ***Mex.***: NovoSeven; ***Neth.***: NovoSeven; ***Norw.***: NovoSeven; ***NZ***: NovoSeven; ***Philipp.***: NovoSeven; ***Pol.***: NovoSeven; ***Port.***: NovoSeven; ***Rus.***: Coagil-VII (Коагил-VII); NovoSeven (НовоСэвен); ***S.Afr.***: NovoSeven; ***Singapore***: NovoSeven; ***Spain***: NovoSeven; ***Swed.***: NovoSeven; ***Switz.***: NovoSeven; ***Thai.***: NovoSeven; ***Turk.***: NovoSeven; ***UK***: NovoSeven; ***Ukr.***: NovoSeven (Новосевен); ***USA***: NovoSeven.

Pharmacopoeial Preparations

Ph. Eur.: Human Coagulation Factor VII.

Factor VIII

AHF; Anthaemophilic Factor; Facteur VIII; Factor antihemofílico A; Антигемофилический Фактор; Фактор VIII.

ATC — B02BD02.

ATC Vet — QB02BD02.

UNII — 839MOZZ4GK (human factor VIII); P89DR4NY54 (recombinant human factor VIII).

Description. Factor VIII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The names Moroctocog Alfa (see below), Octocog Alfa (see below), and Rurioctocog Alfa are in use for recombinant factor VIII.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Coagulation Factor VIII; Factor VIII Coagulationis Humanus; Dried Factor VIII Fraction BP 2014). A sterile freeze-dried preparation of a plasma protein fraction that contains the glycoprotein coagulation factor VIII with varying amounts of von Willebrand factor, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VIII fraction is dissolved in an appropriate liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Auxiliary substances such as a stabiliser may be added. No antimicrobial preservative or antibiotic is added. The specific activity is not less than 1 international unit of factor VIII:C per mg of total protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 20 international units of factor VIII:C per mL.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Human Coagulation Factor VIII (rDNA); Factor VIII Coagulationis Humanus (ADNr)Dried Factor VIII (rDNA) BP 2014). A freeze-dried preparation of glycoproteins having the same activity as coagulation factor VIII in human plasma. It is prepared as full-length factor VIII (octocog alfa), or as a shortened two-chain structure (relative molecular mass 90 000 and 80 000), in which the B-domain has been deleted from the heavy chain (moroctocog alfa). Full-length human rDNA coagulation factor VIII contains 25 potential *N*-glycosylation sites, 19 in the B-domain of the heavy chain, 3 in the remaining part of the heavy chain (relative molecular mass 90 000) and 3 in the light chain (relative molecular mass 80 000).

Human coagulation factor VIII (rDNA) is produced by recombinant DNA technology in mammalian cell culture. Auxiliary substances such as a stabiliser may be added. A white or slightly yellow powder or friable mass. pH of the reconstituted preparation is 6.5 to 7.5. Protect from light.

Moroctocog Alfa *(BAN, rINN)*

Moroctocogum Alfa; Moroktokog Alfa; Moroktokogialfa; Мороктоког Альфа.

(1—742)-(1637—1648)-Blood-coagulation factor VIII (human reduced) complex with 1649—2332-blood-coagulation factor VIII (human reduced).

CAS — 284036-24-4.

UNII — 113E3Z3CJJ.

Pharmacopoeias. *Eur.* (see p. vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Octocog Alfa *(BAN, rINN)*

Bay-w-6240; Factor VIII (rDNA); Octocogum Alfa; Октоког Альфа.

Blood-coagulation factor VIII (human), glycoform α.

CAS — 139076-62-3.

Pharmacopoeias. *Eur.* (see p. vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Units

The potency of factor VIII is expressed in international units and preparations may be assayed using the sixth International Standard for blood coagulation factor VIII concentrate, human (1998).

Uses and Administration

Factor VIII is used as replacement therapy in patients with haemophilia A, a genetic deficiency of factor VIII; it may also be used in acquired haemophilia (see Haemophilias, p. 1126.3).

Preparations of factor VIII may be derived from human plasma or recombinant sources. They are used to control bleeding episodes in the treatment of patients with haemophilia A and to prevent bleeding episodes in such patients undergoing dental and surgical procedures. They may also be used for long-term prophylaxis in patients with severe haemophilia A.

Preparations of factor VIII are given by slow intravenous injection or short infusion, and some octocog alfa preparations may also be given by continuous infusion. The dosage of factor VIII should be determined for each patient and will vary with the circumstances involving bleeding or type of surgery to be performed. In adults, a dose of 1 international unit/kg has been reported to raise the plasma concentration of factor VIII by about 2% (of normal). The response may be lower in children. A suggested formula to calculate, approximately, the dose required for a given effect is:

$$\text{units} = \text{wt (kg)} \times 0.5 \times \%\ \text{desired increase (of normal)}$$

Recommended doses vary depending on the preparation used, but the following increments in plasma concentration of factor VIII have been suggested:

- for mild to moderate haemorrhage an increase to 20 to 30% of normal, usually with a single dose of 10 to 15 units/kg
- for more serious haemorrhage or minor surgery an increase to 30 to 50% of normal, by a usual initial dose of 15 to 25 units/kg followed by 10 to 15 units/kg every 8 to 12 hours if required
- for severe haemorrhage or major surgery an increase to 80 to 100% of normal may be necessary, the usual initial dose being 40 to 50 units/kg followed by 20 to 25 units/kg every 8 to 12 hours. Some octocog alfa preparations may also be given for major surgery as an initial pre-operative bolus followed by a continuous infusion, adjusted postoperatively to daily clearance and desired factor VIII concentrations

For long-term prophylaxis in severe haemophilia A, doses of 10 to 50 units/kg every 2 or 3 days, as required, may be used.

In patients with inhibitory antibodies to human factor VIII, a porcine factor VIII preparation has been used. Its manufacture was discontinued in 2004, but a recombinant product (OBI-1) is in development.

Some factor VIII concentrates also contain von Willebrand factor and these preparations may be used in the management of von Willebrand's disease (p. 1129.3). Commercial very highly purified and recombinant factor VIII preparations do not contain appreciable amounts of von Willebrand factor and are thus ineffective.

Cryoprecipitate is an alternative source of clotting factors and contains factor VIII, factor XIII, von Willebrand factor, fibrinogen, and fibronectin. It has been used in the treatment of haemophilia A and von Willebrand's disease but safer more specific clotting factor alternatives are now available and preferred.

Reviews.

1. McCormack PL, Plosker GL. Octocog alfa, plasma/albumin-free method. *Drugs* 2005; 65: 2613–20.
2. Frampton JE, Wagstaff AJ. Sucrose-formulated octocog alfa: a review of its use in patients with haemophilia A. *Drugs* 2008; 68: 839–53.

Administration. Surgical prophylaxis or significant haemorrhage in patients with haemophilia A is usually managed with injections of factor VIII given intravenously every 8 to 12 hours. However, continuous intravenous infusion has been used as an alternative.[1,2] It prevents wide fluctuations in factor VIII plasma concentrations and there is a progressive decrease in clearance associated with steady state. Studies have suggested that continuous infusion is as effective as bolus injection, but with a lower concentrate requirement. Concerns about continuous infusion include factor VIII stability, bacterial contamination, local irritation and thrombophlebitis, and inhibitor formation.

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; 36: 882–91.
2. Schulman S. Continuous infusion. *Haemophilia* 2003; 9: 368–75.

Adverse Effects and Precautions

Allergic reactions may sometimes follow the use of factor VIII preparations; the chills, urticaria, and headache experienced by some patients may be allergic manifestations. There is the possibility of intravascular haemolysis in patients with blood groups A, B, or AB receiving high doses or frequently repeated doses of factor VIII preparations due to the content of blood group isoagglutinins; also massive doses of some preparations may produce hyperfibrinogenaemia. Such risks should be reduced with more highly purified preparations.

Factor VIII preparations have been associated with the transmission of some viral infections, including hepatitis B and C, and more notably transmission of HIV. Strenuous efforts are now undertaken to screen the donor material from which factor VIII material is obtained and new methods of manufacture have also been introduced with the aim of inactivating any viruses present. Vaccination against hepatitis A and B is recommended for patients not already immune. Recombinant preparations are also available.

Some patients develop antibodies to factor VIII (see Resistance, p. 1149.1).

Effects on blood platelets. There have been case reports of thrombocytopenia associated with use of porcine factor VIII.[1] A retrospective study[2] of patients treated with porcine factor VIII found that the platelet count fell in 61% of 175 infusions given to 57 patients. The fall was generally clinically insignificant and platelet count appeared to recover within an hour. The effect was, however, dose-related, and larger reductions in platelet count were usually associated with intensive replacement over several days for surgery or trauma.

1. Green D, Tuite GF. Declining platelet counts and platelet aggregation during porcine VIII:C infusions. *Am J Med* 1989; 86: 222–4.
2. Hay CRM, *et al.* Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost* 1996; 75: 25–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies factor VIII as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Resistance. Some patients with haemophilia A develop inhibitory antibodies to factor VIII (see Haemophilias, p. 1126.3). The risk is highest within the first 20 to 100 treatments. Low-titre antibodies are usually transient and overcome by increased or continuing treatment with factor VIII. With high-titre highly responding antibodies, however, bleeding episodes may need to be managed with factor VIII inhibitor bypassing fraction (activated prothrombin complex concentrate), or recombinant factor VIIa. Highly responding antibodies can be eradicated by immune tolerance regimens, using regular infusion of factor concentrates over long periods, with additional immunosuppression and immuno-adsorption in some cases.[1] Postmarketing monitoring in Europe has revealed a higher number of cases of inhibitory antibodies associated with recombinant factor VIII preparations than would be expected from experience with plasma-derived products.[2] However, a review[3] by the EMEA found that, on the basis of available data, it was not possible to estimate and compare the incidence of inhibitors between different recombinant factor VIII products. They warned that recurrence of low-titre antibodies had occurred after switching from one product to another in previously treated patients with more than 100 exposure days who had a history of inhibitor development. They also requested that further investigation be undertaken by companies that market recombinant factor VIII products.

There have also been reports of lack of effect with the use of the recombinant factor VIII, moroctocog alfa, for prophylaxis, in patients who have no evidence of antibodies to factor VIII.[4]

1. Bolton-Maggs PHB, Pasi KJ. Haemophilias A and B. *Lancet* 2003; 361: 1801–9.
2. EMEA. EMEA public statement: review of recombinant factor VIII (FVIII) products and inhibitor development: Advate, Kogenate Bayer/Helixate NexGen, Kogenate/Helixate, Recombinate, ReFacto (issued 18th October, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/02/WC500074387.pdf (accessed 13/08/10)
3. EMEA. Public statement: EMEA completes the review of recombinant factor VIII products and inhibitor development (issued 31st July, 2007). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500011389.pdf (accessed 13/08/10)
4. Wyeth Canada. Important safety information about Refacto (moroctocog alfa), antihemophilic factor (recombinant) [BDDrFVIII] (issued 15th September, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/refacto_hpc-cps-eng.pdf (accessed 29/08/08)

Transmission of infections. Treatment with heat or chemicals and efforts to screen the donor material from which factor VIII and other clotting factors are obtained seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses, such as human parvovirus B19 and hepatitis A, may still be transmitted. Vaccination against hepatitis A and B has been recommended for all patients who receive or may require blood products. Plasma-derived clotting factor preparations, or recombinant preparations containing added albumin, may carry a risk of transmission of variant Creutzfeldt-Jakob disease (see under Blood, p. 1135.3). There has also been some concern about the use of human and animal products in the culture media used to manufacture recombinant clotting factor preparations, because of the theoretical risk of viral transmission from infected cell lines. Recombinant manufacturing techniques and formulations have changed over time and human and animal products are no longer used in some preparations.[1]

1. Keeling D, *et al.* United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO). Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2008; 14: 671–84. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2008.01695.x/pdf (accessed 13/08/10)

Pharmacokinetics

In patients with haemophilia A, factor VIII preparations have a terminal half-life of about 12 hours, whether human-derived or of recombinant origin.

References.
1. Messori A, *et al.* Clinical pharmacokinetics of factor VIII in patients with classic haemophilia. *Clin Pharmacokinet* 1987; 13: 365–80.
2. Björkman S, *et al.* Pharmacokinetics of factor VIII in humans: obtaining clinically relevant data from comparative studies. *Clin Pharmacokinet* 1992; 22: 385–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Advate; Beriate P; Emoclot; Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Immunate; Koate-DVI; Kogenate; Monoclate-P; Octanate; Optivate; Recombinate; *Austral.*: Biostate; Kogenate; Recombinate; ReFacto†; Xyntha; *Austria*: Advate; Beriate; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate†; ReFacto; Wilate; *Belg.*: Advate; Factane; Haemate; Helixate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Braz.*: Beriate P†; Haemate; Hemofil; Immunate; Koate; Kogenate; Monoclate-P†; Recombinate; *Canad.*: Advate; Helixate; Humate-P; Kogenate; Recombinate†; ReFacto†; Wilate; Xyntha; *Chile*: Emoclot; Fanhdi; Koate-DVI†; Kogenate; *China*: Haimo Laishi (海莫莱士); Kang Si Ping (康斯平); Kogenate (拜科奇); *Cz.*: Advate; Fanhdi; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Denm.*: Advate; Haemate; Helixate; Kogenate; Octanate; ReFacto; Wilnativ; *Fin.*: Advate; Amofil; Haemate; Immunate; Kogenate; Octafil; Recombinate; ReFacto; Wilate; *Fr.*: Advate; Factane; Helixate; Hemofil M†; Kogenate; Monoclate-P†; Octanate; Recombinate†; ReFacto; *Ger.*: Advate; Beriate; Fanhdi; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Gr.*: 8 Y; Advate; Fanhdi; Haemate; Haemoctin; Helixate; Hemofil M; Hyate:C†; Immunate; Koate-HP; Kogenate; Monoclate-P; Octanate; Recombinate; ReFacto; *Hong Kong*: Aleviate; Alphanate; Biostate; Haemate†; Hemofil M; Koate-DVI; Kogenate; Recombinate; *Hung.*: Advate; Beriate P; Fanhdi†; Haemate; Haemoctin SDH; Helixate; Humafactor-8; Immunate; Kogenate; Octanate; Recombinate; ReFacto; *India*: Emoclot; Fanhdi; Haemoctin SDH; Hemofil M; Iort3; Monoclate P; *Indon.*: Koate; Kogenate; *Irl.*: Advate; Fanhdi; Helixate; Kogenate; Octanate; ReFacto; Wilate; *Israel*: Fanhdi; Haemate; Haemoctin SDH; Helixate; Hemofil M; Immunate; Koate; Kogenate; Monarc-M†; Monoclate-P†; Octanate; Optivate; Recombinate; ReFacto†; Wilate; Xyntha; *Ital.*: Advate; Alphanate; Beriate P; Emoclot; Fanhdi; Haemate; Haemoctin; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Talate; *Jpn*: Advate; Recombinate; *Malaysia*: Advate; Aleviate; Alphanate; Fanhdi†; Hemofil†; Kogenate; *Mex.*: Beriate P; Kogenate; Monoclate-P†; Octanate; Optivate; *Neth.*: Aafact; Advate; Alphanate; Bioclate†; Haemate; Haemoctin; Helixate; Hemofil†; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Norw.*: Advate; Haemate; Helixate; Kogenate; Octanate; ReFacto; Wilate; *NZ*: Advate; AHF†; Biostate; Kogenate; Octanate; Recombinate; ReFacto†; Wilate; Xyntha; *Philipp.*: Alphanate; Hemofil M; Koate-DVI; *Pol.*: Czynnik VIII (Metoda M)†; Haemoctin†; Helixate; Hemofil; Immunate; Kogenate; ReFacto; *Port.*: Advate; Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH†; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Rus.*: Beriate (Бериате); Emoclot (Эмоклот); Fanhdi (Фанди); Haemoctin (Гемоктин); Hemofil (Гемофил); Immunate (Иммунат); Koate (Кожйт-ДВИ); Kogenate (Когенэйт); LongEight (ЛонгЭйт); Octanate (Октанат); Wilate (Вилате); *S.Afr.*: Haemosolvate; *Singapore*: Alphanate; Biostate; Fanhdi; Haemoctin SDH; Hemofil M; Kogenate; Optivate; *Spain*: Advate; Beriate P; Fanhdi; Haemate; Haemoctin; Helixate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Swed.*: Advate; Haemate; Helixate; Immunate; Kogenate; Octanate; Octonativ-M†; Recombinate; ReFacto; Wilate; *Switz.*: Advate; Beriate; Haemate; Haemoctin; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; *Thai.*: Alphanate; Emoclot; Fanhdi†; Haemoctin SDH; Hemofil M; Hemoraas; Immunate; Kogenate; Method M; Octanate; Recombinate; *Turk.*: Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH; Haemoetin†; Hemofil M; Immunate; Koate-DVI; Kogenate; Liberate; Monarc-M†; Octanate; Octavi; Recombinate; *UK*: Advate; Alphanate; Beriate P; Fanhdi; Haemate; Helixate; Hyate:C†; Kogenate; Monoclate-P; Octanate; Optivate; Recombinate; ReFacto; Replenate; Wilate; *Ukr.*: BioKlot (БиоКлот); ReFacto (РеФакто); *USA*: Advate; Alphanate; Helixate; Hemofil M; Humate-P; Koate-DVI; Kogenate; Monarc-M†; Monoclate-P; Recombinate; ReFacto; Wilate; Xyntha; *Venez.*: Fandhi.

Multi-ingredient Preparations. *Arg.*: Eluage; Wilate.

Pharmacopoeial Preparations
Ph. Eur.: Human Coagulation Factor VIII (rDNA); Human Coagulation Factor VIII.

Factor VIII Inhibitor Bypassing Fraction

Activated Prothrombin Complex Concentrate; Anti-inhibitor Coagulant Complex; Complejo coagulante antiinhibidor del factor VIII; Faktör VIII İnhibitör Baypaslayan Fraksiyonu; Антиингибиторный Коагулянтный Комплекс.

ATC — B02BD03.
ATC Vet — QB02BD03.
UNII — CS849DUN3M.

Uses and Administration

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma and contain factors II, IX, and X, and activated factor VII; small amounts of factor VIII and factors of the kallikrein-kinin system are also present. They are used in patients with haemophilia A who have antibodies to factor VIII and in patients with acquired antibodies to factor VIII (see Haemophilias, p. 1126.3). The dose is given intravenously and depends on the preparation used.

References.
1. White GC. Seventeen years' experience with Autoplex/Autoplex T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at a major haemophilia centre. *Haemophilia* 2000; 6: 508–12.
2. Wilde JT. Evidence for the use of activated prothrombin complex concentrates (aPCCs) in the treatment of patients with haemophilia and inhibitors. *Pathophysiol Haemost Thromb* 2002; 32 (suppl): 9–12.
3. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia* 2004; 10: 169–73.
4. Perry D, *et al.* FEIBA prophylaxis in haemophilia patients: a clinical update and treatment recommendations. *Haemophilia* 2010; 16: 80–9.

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of preparations with factor VIII inhibitor bypassing activity. Rapid infusion may cause headache, flushing, and changes in blood pressure and pulse rate.

It should not be given if disseminated intravascular coagulation is suspected or if there are signs of fibrinolysis. It should be used with caution in patients with liver disease. The risk of thromboembolism may be increased with the use of high doses or in patients with thrombotic risk factors.

As with other plasma-derived products, there is a risk of transmission of infection.

References.
1. Ehrlich HJ, *et al.* Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. *Haemophilia* 2002; 8: 83–90.
2. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. *Haemophilia* 2004; 10 (suppl): 10–16.
3. Aledort LM. Factor VIII inhibitor bypassing activity (FEIBA) – addressing safety issues. *Haemophilia* 2008; 14: 39–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies factor VIII inhibitor bypassing fraction as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Feiba; *Austria*: Feiba; *Belg.*: Confidex; Feiba; *Braz.*: Feiba; *Canad.*: Feiba; *Chile*: Feiba; *Cz.*: Feiba; Ocplex; *Denm.*: Feiba; *Fin.*: Confidex; Feiba; *Fr.*: Feiba; *Ger.*: Feiba; *Gr.*: Feiba; *Hung.*: Feiba; *Israel*: Feiba; *Ital.*: Feiba; *Malaysia*: Feiba†; *Neth.*: Feiba; *Norw.*: Confidex; Feiba; *NZ*: Feiba; *Pol.*: Feiba; *Port.*: Feiba; *Rus.*: Feiba (Фейба); *S.Afr.*: Feiba; *Spain*: Feiba; *Swed.*: Confidex; Feiba; Ocplex; *Switz.*: Feiba; *Thai.*: Feiba; *Turk.*: Feiba; *UK*: Feiba; *USA*: Feiba.

Factor IX

Christmas Factor; Facteur IX; Factor antihemofílico B; Factor Christmas; Plasma Thromboplastin Component; PTC; Фактор IX.

ATC — B02BD04.
ATC Vet — QB02BD04.
UNII — 6U90Y1795T (human factor IX); FW411QXD5M (factor IX complex).

Description. Factor IX is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Nonacog Alfa is in use for recombinant factor IX.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Human Coagulation Factor IX; Factor IX Coagulationis Humanus; Dried Factor IX Fraction BP 2014). A sterile freeze-dried preparation of a plasma protein fraction containing coagulation factor IX, prepared by a method that effectively separates it from other prothrombin complex factors (factors II, VII, and X). It is prepared from human plasma obtained from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed to maintain functional integrity of factor IX, to minimise activation of any coagulation factor, and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor IX fraction is dissolved in a suitable liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. Heparin, antithrombin, or other auxiliary substances such as a stabiliser may be included. No antimicrobial preservative or antibiotic is added. The specific activity is not less than 50 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

Ph. Eur. 8: (Human Prothrombin Complex; Prothrombinum Multiplex Humanum; Dried Prothrombin Complex BP 2014). A sterile plasma protein fraction containing human coagulation factor IX with variable amounts of coagulation factors II, VII, and X. It is prepared by fractionation of human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface

The symbol † denotes a preparation no longer actively marketed

antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed in particular to minimise thrombogenicity and includes a step or steps that have been shown to remove or inactivate known agents of infection. The prothrombin complex fraction is dissolved in a suitable liquid, sterilised by filtration, distributed aseptically into final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. No antimicrobial preservative or antibiotic is added. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. The potency of the preparation is not less than 0.6 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or slightly coloured, very hygroscopic, powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

USP 36: (Factor IX Complex). A sterile freeze-dried powder consisting of partially purified factor IX fraction, as well as concentrated factor II, VII, and X fractions of venous plasma obtained from healthy human donors. It contains no preservatives. It should be stored at 2 degrees to 8 degrees in hermetically-sealed containers. It should be used within 4 hours after reconstitution and administered with equipment that includes a filter.

Nonacog Alfa *(BAN, USAN, rINN)*

Nonacogum Alfa; Nonakog Alfa; Nonakogialfa; Нонаког Альфа.

Blood-coagulation factor IX (human), glycoform α; Blood-coagulation factor IX (synthetic human).

CAS — 113478-33-4; 181054-95-5.
ATC — B02BD09.
ATC Vet — QB02BD09.
UNII — 382L14738L.

Units

The activity of factor IX is expressed in terms of international units and preparations may be assayed using the third International Standard for blood coagulation factor IX concentrate, human (1996).

Uses and Administration

Factor IX is used as replacement therapy in patients with haemophilia B (Christmas disease), a genetic deficiency of factor IX (see Haemophilias, p. 1126.3).

There are two forms of factor IX preparation derived from plasma; one is of high purity, the other is rich in other clotting factors (prothrombin complex concentrates). A recombinant factor IX preparation, nonacog alfa, is also available. Preparations that contain other factors as well as factor IX may sometimes be useful for the treatment of bleeding due to deficiencies of factors II, VII, and X, as well as IX, and in the preparation of such patients for surgery; they may also be used for immediate reversal of coumarin anticoagulants and in the management of patients with haemophilia A who have antibodies to factor VIII.

Factor IX is given by slow intravenous infusion. In patients with factor IX deficiency the dosage should be determined for each patient and will vary with the preparation used and the circumstances of bleeding or type of surgery to be performed. Suggested target factor IX concentrations for patients with haemophilia B vary, but the following have been suggested:

- for mild to moderate haemorrhage the plasma concentration of factor IX should be raised to 20 to 30% of normal
- for more serious haemorrhage or minor surgery it should be raised to 30 to 60% of normal
- for severe haemorrhage or major surgery an increase to 60 to 100% of normal may be necessary

Calculation of the appropriate dose varies according to the manufacturers' recommendations.

For long-term prophylaxis in severe haemophilia B, doses of 20 to 40 international units/kg every 3 or 4 days, as required, may be used.

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of factor IX preparations and there may be chills and urticaria. Other adverse effects include nausea and vomiting, headache, and flushing particularly after rapid infusion. Intravascular coagulation and thrombosis have been reported, mainly in patients with liver disease, and factor IX should be used with care in patients at risk of thromboembolism or disseminated intravascular coagulation. The risk should be less with more highly purified preparations.

As with other plasma derivatives there is a possibility of transmitting viral infection, although selection of donors and heat or chemical treatments of products are used to minimise the risk. Vaccination against hepatitis A and B is recommended for patients not already immune.

Antibodies to factor IX may develop rarely.

Effects on the cardiovascular system. Some factor IX preparations derived from plasma contain other clotting factors in addition to factor IX (prothrombin complex concentrates), and some preparations have also contained activated clotting factors. Such preparations have the potential to produce thromboembolic complications.[1,2] Reported complications include arterial and venous thrombosis, pulmonary embolism, acute myocardial infarction, and disseminated intravascular coagulation. Risk factors in haemophiliacs include liver disease, severe muscle haemorrhages, crush injuries, immobilisation, and orthopaedic surgery. Rapid infusion of factor IX concentrates, or repeated large doses, may also increase the risk of thromboembolism. The risks of thromboembolism have been reduced with the development of more purified prothrombin complex concentrates, and highly purified factor IX preparations that do not contain other clotting factors.[1,3]

1. Köhler M. Thrombogenicity of prothrombin complex concentrates. *Thromb Res* 1999; 95 (suppl): S13–S17.
2. Najaf SM, *et al.* Myocardial infarction during factor IX infusion in hemophilia B: case report and review of the literature. *Ann Hematol* 2004; 83: 604–7.
3. Santagostino E, *et al.* Markers of hypercoagulability in patients with hemophilia B given repeated, large doses of factor IX concentrates during and after surgery. *Thromb Haemost* 1994; 71: 737–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies factor IX as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] NAPOS has not yet classified nonacog alfa or prothrombin complex concentrates.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aimafix; Benefix; Berinin P; Beriplex PN; Immunine; Mononine; Octanine; Protromplex; Replenine-VF; ***Austral.***: Benefix; Monofix-VF; ***Austria***: Benefix; Beriplex PN; Cofact; Haemonine; Immunine; Mononine; Octanine; Octaplex; Prothromplex Partiell; Prothrompiex S-TIM 4†; Prothromplex TOTAL; ***Belg.***: Benefix; Mononine; Nonafact; Octanine; Octaplex; PPSB Conc SD; ***Braz.***: Berinin†; Beriplex PN; Immunine; Mononine†; Octaplex; Prothrompiex-T; ***Canad.***: Benefix; Beriplex PN; Immunine; Mononine†; Octaplex; ***Chile***: Aimafix; ***China***: Pushu Laishi (普舒莱士); ***Cz.***: Benefix; Immunine; Mononine; Nonafact; Octanine; Prothromplex; ***Denm.***: Benefix; Nanofix; Nanotiv†; Octaplex; ***Fin.***: Benefix; Cofact; Nonafact; Octanine; Octaplex; ***Fr.***: Benefix; Betafact; Kanokad; Kaskadil†; Mononine; Octafix; Octaplex; ***Ger.***: Alphanine; Benefix; Berinin; Beriplex PN; Cofact; Haemonine; Immunine; Mononine; Octanine; Octaplex; PPSB Konzentrat S-TIM†; PPSB-human; ***Gr.***: Benefix; Beriplex PN; Betafact; Haemonine; Immunine; Mononine; Replenine; ***Hong Kong***: Alphanine; Benefix; Monofix-VF; Profilnine; Proplex T†; Prothrombinex; ***Hung.***: Benefix; Berinin P; Beriplex PN; Humafactor-9; Immunine†; Octanine F; Prothromplex; ***India***: Immunine; ***Indon.***: Cofact; ***Irl.***: Benefix; Immunine; Nanofix; Nanotiv†; Nonafact; Octaplex; ***Israel***: Benefix; Beriplex; Betafact; Mononine; Nanotiv†; Octaplex; Proplex†; Replenine; ***Ital.***: Aimafix; Alphanine†; Benefix; Immunine; Mononine; Protromplex TIM 3; Uman-Complex DI; ***Malaysia***: Alphanine; Profilnine; Replenine; ***Mex.***: Berinin P; Octanine F; Replenine†; ***Neth.***: Alphanine; Benefix; Beriplex PN; Betafact; Cofact; Immunine; Mononine; Nanotiv†; Nonafact; Octaplex; ***Norw.***: Benefix; Immunine; Nanotiv†; Octanine; Octaplex; Prothromplex; ***NZ***: Benefix; Monofix; Pronativ; Prothrombinex; ***Philipp.***: Alphanine†; Profilnine; ***Pol.***: Benefix; Immunine; Nonafact; Prothromplex; ***Port.***: Aimafix; Benefix; Beriplex; Betafact; Immunine; Mononine; Nanotiv; Nonafact; Octaninef; Octaplex; ***Rus.***: Aimafix (Аймафикс); Immunine (Иммунин); Octanine (Октанайн); Protromplex (Протромплекс); Replenin-VF (Репленин-ВФ); ***S.Afr.***: Haemosolvex; Prothromplex-T TIM 4†; ***Singapore***: Alphanine; Monofix-VF; Profilnine; Replenine; ***Spain***: Benefix; Berinin P; Beriplex; Immunine; Mononine; Nanotiv†; Novix; Octanine; Octaplex; Prothromplex; ***Swed.***: Benefix; Immunine; Mononine; Nanofix; Nanotiv†; ***Switz.***: Benefix; Berinin; Beriplex; Immunine; Octanine F; Octaplex; Prothromplex; ***Thai.***: Aimafix; Alphanine; Immunine; Octanine; Profilnine; ***Turk.***: Aimafix; Berinin P; Betafact; Cofact; Immunine; Kaskadil; Konynet; Nonafact; Octanine F; Octanyne; Reblenine; Replenine; ***UK***: Alphanine; Benefix; Beriplex PN; Mononine; Octaplex; Replenine; ***Ukr.***: Benefix (БенеФикс); ***USA***: Alphanine; Bebulin VH; Benefix; Kcentra; Mononine; Profilnine; Proplex T†; Rixubis.

Multi-ingredient Preparations. ***Rus.***: Uman-Complex DI (Уман-Комплекс ДИ).

Pharmacopoeial Preparations

Ph. Eur.: Human Coagulation Factor IX; Human Prothrombin Complex;

USP 36: Factor IX Complex.

Factor XI

Facteur XI; Plasma Thromboplastin Antecedent; PTA; Фактор XI.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Human Coagulation Factor XI; Factor XI Coagulationis Humanus; Dried Factor XI Fraction BP 2014). A plasma protein fraction that contains coagulation factor XI. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor XI fraction is dissolved in a suitable liquid, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under nitrogen. Heparin, C_1-esterase inhibitor, and antithrombin III, may be added. No antimicrobial preservative is added. When reconstituted as stated on the label the resulting solution contains not less than 50 units/mL.

A white or almost white powder or friable solid. pH of the reconstituted preparation is 6.8 to 7.4. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Factor XI is used as replacement therapy in patients with congenital factor XI deficiency (haemophilia C; see Inherited Haemorrhagic Disorders, p. 1128.2) for the prevention and treatment of haemorrhage. The dose is based on the degree of factor XI deficiency and the condition of the patient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Hemoleven; ***Gr.***: Hemoleven.

Factor XIII

Fibrin-stabilising Factor; FSF; Фактор XIII.

ATC — B02BD07.
ATC Vet — QB02BD07.
UNII — F7R0FBC1XD.

Description. Factor XIII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Catridecacog is in use for recombinant factor XIII A-subunit.

Catridecacog *(rINN)*

Catridécacog; Catridecacogum; NN-1841; Катридекаког.

Human factor XIII $[A_2]$ homodimer (allele F13A*1B, recombinant DNA origin.

CAS — 606138-08-3.
ATC — B02BD11.
ATC Vet — QB02BD11.
UNII — NU23Q531G1.

Uses and Administration

Factor XIII is used as replacement therapy in patients with a genetic deficiency of factor XIII (see Inherited Haemorrhagic Disorders, p. 1128.2). It may also be used in patients with acquired deficiency of factor XIII, and for supportive therapy in postoperative wound healing.

Factor XIII derived from human plasma is given by slow intravenous injection or infusion. Licensed dosage recommendations for prophylaxis of haemorrhage in patients with genetic deficiency vary between countries, but are based on the degree of deficiency and the condition of the patient. In Europe, about 10 units/kg may be given once a month. The interval between doses may be shortened if spontaneous haemorrhage occurs. In the USA, an initial dose of 40 units/kg is given once every 4 weeks, and adjusted in steps of 5 units/kg to maintain a trough factor XIII activity level of between 5 and 20%. Factor XIII is also licensed in some European countries for pre-operative prophylaxis and for treatment of bleeding episodes. For pre-operative use, a dose of up to 35 units/kg may be given immediately before the operation and followed by adequate doses to maintain efficacy until the wound is healed. For the treatment of severe bleeding episodes and extensive haematomas 10 to 20 units/kg should be given daily, until bleeding stops. In acute bleeding, especially intracranial

bleeding, doses of up to 50 units/kg may be needed to raise factor XIII to normal levels. Doses of at least 15 to 20 units/kg daily may be required for the treatment of haemorrhage in acquired factor XIII deficiency.

In the promotion of postoperative wound healing, a dose of 10 units/kg may be given on the day of the operation and on each of the next 3 days; in some cases a dose of up to 20 units/kg may be used.

Cryoprecipitate is also used as a source of factor XIII.

Factor XIII is also a component of fibrin glues (see Fibrin, below).

Catridecacog is a recombinant factor XIII A-subunit. It is structurally identical to human factor XIII A subunit [A_2] and is used in the prophylactic treatment of bleeding in patients, aged 6 years or more, with congenital factor XIII A-subunit deficiency. The recommended dose of 35 units/kg is given once each month by slow intravenous bolus injection. Dose adjustment may be made based on factor XIII activity levels.

References.
1. Lim W, *et al.* Prophylactic and perioperative replacement therapy for acquired factor XIII deficiency. *J Thromb Haemost* 2004; **2**: 1017–19.
2. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia* 2008; **14**: 1190–1200.
3. Inbal A, *et al.* Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012; **119**: 5111–17.

Inflammatory bowel disease. Some patients with inflammatory bowel disease (p. 1811.3) may be deficient in factor XIII, possibly due to increased intestinal blood loss seen in severe ulcerative colitis or increased mucosal deposition of factor XIII in Crohn's disease. Factor XIII concentrate given intravenously has produced beneficial results in 12 patients with active ulcerative colitis resistant to conventional therapy with corticosteroids and mesalazine[1] and has also been associated with healing of intractable fistulae in 3 of 4 patients with Crohn's disease.[2] However, a controlled study[3] found no benefit from factor XIII in active corticosteroid-refractory ulcerative colitis.

1. Lorenz R, *et al.* Factor XIII substitution in ulcerative colitis. *Lancet* 1995; **345**: 449–50.
2. Oshitani N, *et al.* Treatment of Crohn's disease fistulas with coagulation factor XIII. *Lancet* 1996; **347**: 119–20.
3. Bregenzer N, *et al.* Lack of clinical efficacy of additional factor XIII treatment in patients with steroid refractory colitis. *Z Gastroenterol* 1999; **37**: 999–1004.

Wounds and ulcers. Topical factor XIII has been reported to promote wound healing in patients with refractory leg ulcers.[1-3]

1. Wozniak G, *et al.* Factor XIII in ulcerative leg disease: background and preliminary clinical results. *Semin Thromb Hemost* 1996; **22**: 445–50.
2. Herouy Y, *et al.* Factor XIII-mediated inhibition of fibrinolysis and venous leg ulcers. *Lancet* 2000; **355**: 1970–1.
3. Hildenbrand T, *et al.* Treatment of nonhealing leg ulcers with fibrin-stabilizing factor XIII: a case report. *Dermatol Surg* 2002; **28**: 1098–9.

Adverse Effects and Precautions

Like other clotting factor preparations (see Factor VIII, p. 1148.3), the use of plasma-derived factor XIII may be associated with risks of hypersensitivity reactions, thrombosis, and viral infection transmission. Inhibitors of factor XIII may occur very rarely.

Headache has been reported as a common adverse effect of catridecacog. Risks of hypersensitivity and thrombosis also exist. Catridecacog should not be given to patients who have developed neutralising antibodies to factor XIII without close monitoring.

Catridecacog is not effective for prophylaxis in patients with factor XIII B-subunit deficiency.

Pharmacokinetics

In patients with congenital factor XIII deficiency, catridecacog has an estimated half-life of 11.8 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fibrogammin P; *Austria*: Fibrogammin; *Belg.*: Fibrogammin; *Braz.*: Fibrogammin; *Denm.*: Novothirteen; *Fr.*: Fibrogammin; *Ger.*: Fibrogammin; *Gr.*: Fibrogammin; *Hong Kong*: Fibrogammin P†; *Israel*: Fibrogammin; *Switz.*: Fibrogammin; Novothirteen; *UK*: Fibrogammin P; *USA*: Corifact.

Multi-ingredient Preparations. *Arg.*: Beriplast P; Tissucol; *Austral.*: Tisseel Duo†; *Austria*: Beriplast; Tissucol Duo Quick†; Tissucol†; *Belg.*: Tissucol Duo; Tissucol Kit; *Braz.*: Beriplast P; *Canad.*: Tisseel; *Chile*: Beriplast P†; *Cz.*: Tissucol; *Denm.*: Tisseel Duo Quick; *Fin.*: Tisseel Duo Quick; *Fr.*: Beriplast; Tissucol; *Ger.*: Beriplast; Tissucol Duo S; Tissucol-Kit; *Gr.*: Beriplast; *Hong Kong*: Beriplast P; Tisseel; *Hung.*: Beriplast P; Tissucol-Kit; *Indon.*: Beriplast; *Irl.*: Tisseel; *Israel*: Beriplast†; Tisseel†; *Ital.*: Beriplast; *Jpn*: Bolheal; *Mex.*: Beriplast P; *Neth.*: Beriplast P; Tisseel; Tissucol Duo; Tissucol; *Norw.*: Tisseel; *NZ*: Tisseel Duo; *Pol.*: Beriplast; *Port.*: Tissucol Duo†; *Rus.*: Tissucol Kit (Тиссукол Кит); *Spain*: Beriplast P Combi; Tissucol Duo; *Swed.*: Tisseel Duo Quick; *Switz.*: Beriplast P; Tisseel; Tissucol Duo S†; Tissucol†; *Turk.*: Beriplast P; *UK*: Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit.

Fibrin *(rINN)*

Fibrina; Fibrine; Fibrinum; Фибрин.

Pharmacopoeias. Many pharmacopoeias have monographs for fibrin preparations, including *Eur.* (see p. vii).

Ph. Eur. 8: (Fibrin Sealant Kit: Fibrini Glutinum). It is composed of two components, a fibrinogen concentrate containing human fibrinogen (component 1), and a human thrombin preparation (component 2). The kit may also contain other ingredients, such as human factor XIII, a fibrinolysis inhibitor, or calcium ions. Stabilisers such as human albumin may be added. The human constituents are obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The constituents are passed through a bacteria-retentive filter and distributed aseptically into sterile containers. Containers of freeze-dried constituents are sealed under vacuum or filled with oxygen-free nitrogen or other suitable inert gas before sealing. No antimicrobial preservative is added. When thawed or reconstituted as stated on the label, the fibrinogen concentrate contains not less than 40 g/litre of clottable protein; the activity of the thrombin preparation varies over a wide range (about 4 to 1000 international units/mL). Protect from light.

Profile

Fibrin glue is prepared by mixing solutions containing fibrinogen, thrombin, and calcium ions, with the addition of aprotinin to inhibit fibrinolysis. It may also include factor XIII and other clotting components. Fibrin glue is used as a haemostatic to control haemorrhage during surgical procedures or as a spray to bleeding surfaces. Some preparations are used for autologous skin-graft adhesion in the management of burns.

A dry artificial sponge of human fibrin, known as human fibrin foam, has been used similarly as a haemostatic; it is prepared by clotting human thrombin with a foam of human fibrinogen solution. A collagen sponge coated with thrombin and fibrinogen is also available to promote haemostasis and tissue sealing, and to provide suture support in vascular surgery.

Adverse effects. Fatal neurotoxicity has been reported[1] after the use of a fibrin sealant during neurosurgical procedures. The toxicity may have been due to the presence of tranexamic acid as a stabiliser in the formulation, and such formulations should not be used in surgical operations where contact with the CSF or dura mater could occur.[2]

For rare reports of hypersensitivity reactions to aprotinin used locally as a component of fibrin sealant, see p. 1134.3.

1. CSM/MCA. Quixil human surgical sealant: reports of fatal reactions. *Current Problems* 1999; **25**: 19. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)
2. CSM/MCA. Quixil human surgical sealant: update on fatal neurotoxic reactions. *Current Problems* 2000; **26**: 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074606&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)

Use. Reviews.

1. Dunn CJ, Goa KL. Fibrin sealant: a review of its use in surgery and endoscopy. *Drugs* 1999; **58**: 863–86.
2. Carless PA, *et al.* Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 03/06/05).
3. MacGillivray TE. Fibrin sealants and glues. *J Card Surg* 2003; **18**: 480–5.
4. Fattahi T, *et al.* Clinical applications of fibrin sealants. *J Oral Maxillofac Surg* 2004; **62**: 218–24.
5. Schexneider KI. Fibrin sealants in surgical or traumatic hemorrhage. *Curr Opin Hematol* 2004; **11**: 323–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Kang Pu Xin (康普欣).

Multi-ingredient Preparations. *Arg.*: Beriplast P; Tissucol; *Austral.*: Tisseel Duo†; *Austria*: Beriplast; Evicel; TachoSil; Tisseel; Tissucol Duo Quick†; Tissucol†; *Belg.*: Artiss; TachoSil; Tissucol Duo; Tissucol Kit; *Braz.*: Beriplast P; TachoSil; *Canad.*: Artiss; Tisseel; *Chile*: Beriplast P†; *Cz.*: Artiss; Evicel; TachoSil; Tisseel; Tissucol; *Denm.*: Artiss; Evicel; TachoSil; Tisseel Duo Quick; *Fin.*: Artiss; TachoSil; Tisseel Duo Quick; Tisseel; *Fr.*: Artiss; Beriplast; Evicel; TachoSil; Tissucol; *Ger.*: Artiss; Beriplast; Evicel; TachoSil; Tissucol Duo S; Tissucol-Kit; *Gr.*: Beriplast; Evicel; TachoSil; Tisseel; *Hong Kong*: Beriplast P; Tisseel; *Hung.*: Beriplast P; TachoSil; Tissucol-Kit; *Indon.*: Beriplast; Evicel; TachoSil; Tisseel; *Israel*: Beriplast†; Evicel; TachoSil; Tisseel†; *Ital.*: Beriplast; TachoSil; Tissucol; *Jpn*: TachoSil; *Mex.*: Beriplast P; *Neth.*: Artiss; Beriplast P; TachoSil; Tisseel; Tissucol Duo; Tissucol; *Norw.*: Artiss; Evicel; TachoSil; Tisseel; *NZ*: Tisseel Duo; *Pol.*: Beriplast; Evicel; TachoSil; *Port.*: Evicel; TachoSil; Tissucol Duo†; *Rus.*: Tissucol Kit (Тиссукол Кит); *Spain*: Artiss; Beriplast P Combi; Evicel; TachoSil; Tissucol Duo; *Swed.*: Artiss; Evicel; TachoSil; Tisseel Duo Quick; *Switz.*: Artiss; Beriplast P; Evicel; TachoSil; Tisseel; Tissucol Duo S†; Tissucol†; *Thai.*: Tisseel; *Turk.*: Beriplast P; *UK*: TachoSil; Tisseel; *USA*: Artiss; Evicel; TachoSil; Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit.

Fibrinogen

Factor I; Fibrinogène; Fibrinógeno; Fibrinogenum; Fibrinojen; Fibrynogen.
ATC — B02BB01; B02BC10.
ATC Vet — QB02BB01.
UNII — N94833051K (human fibrinogen).

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Fibrinogen; Fibrinogenum Humanum). A sterile freeze-dried preparation of a plasma protein fraction containing the soluble constituent of human plasma that is transformed to fibrin on addition of thrombin. It is obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Stabilisers, including protein such as human albumin, salts, and buffers may be added. No antimicrobial preservative or antibiotic is added. When dissolved in the volume of solvent stated on the label, the solution contains not less than 10 g/litre of fibrinogen.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

Fibrinogen has been used to control haemorrhage associated with low blood-fibrinogen concentration in afibrinogenaemia or hypofibrinogenaemia although plasma or cryoprecipitate is usually preferred. Fibrinogen has also been used in disseminated intravascular coagulation (p. 1126.1). It is a component of fibrin glue (see Fibrin, above). Recombinant human fibrinogen is under investigation.

Fibrinogen labelled with radionuclides has also been used in diagnostic procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: RiaSTAP; *Austria*: Haemocomplettan; *Belg.*: Riastap; *Braz.*: Haemocomplettan; *China*: Fabu Laishi (法布莱士); *Cz.*: Haemocomplettan; *Denm.*: Riastap; *Fin.*: Riastap; *Fr.*: Clottafact; Clottagen†; Haemocomplettan†; Riastap; *Ger.*: Haemocomplettan; *Gr.*: Haemocomplettan; *Hung.*: Haemocomplettan; *India*: Fibroraas; *Irl.*: Riastap; *Israel*: Haemocomplettan; *Neth.*: Haemocomplettan; *Norw.*: Riastap; *Port.*: Haemocomplettan; *Spain*: RiaSTAP; *Swed.*: Riastap; *Switz.*: Haemocomplettan; *Thai.*: Fibroraas; *Turk.*: Haemocomplettan; *UK*: Riastap; *USA*: RiaSTAP.

Multi-ingredient Preparations. *Arg.*: Beriplast P; Tissucol; *Austral.*: Tisseel Duo†; *Austria*: Beriplast; Evicel; TachoSil; Tisseel; Tissucol Duo Quick†; Tissucol†; *Belg.*: Artiss; Quixil†; TachoSil; Tissucol Duo; Tissucol Kit; *Braz.*: Beriplast P; TachoSil; *Canad.*: Artiss; Tisseel; *Chile*: Beriplast P†; *China*: FibinGluRAAS (护固莱士); *Cz.*: Artiss; Evicel; TachoSil; Tisseel; Tissucol; *Denm.*: Artiss; Evicel; Quixil; TachoSil; Tisseel Duo Quick; *Fin.*: Artiss; Quixil; TachoSil; Tisseel Duo Quick; Tisseel; *Fr.*: Artiss; Beriplast; Evicel; TachoSil; Tissucol; *Ger.*: Artiss; Beriplast; Evicel; Quixil; TachoSil; Tissucol Duo S; Tissucol-Kit; *Gr.*: Beriplast; Evicel; TachoSil; Tisseel; *Hong Kong*: Beriplast P; TachoComb; Tisseel; *Hung.*: Beriplast P; TachoSil; Tissucol-Kit; *Indon.*: Beriplast; *Irl.*: Artiss; Evicel; TachoSil; *Israel*: Beriplast†; TachoSil; Tisseel†; *Ital.*: Beriplast; Quixil; TachoSil; *Jpn*: Bolheal; TachoSil; *Mex.*: Beriplast P; *Neth.*: Artiss; Beriplast P; Quixil†; TachoSil; Tisseel; Tissucol Duo; Tissucol; *Norw.*: Artiss; Evicel; TachoSil; Tisseel; *NZ*: Tisseel Duo; *Pol.*: Beriplast; Evicel; TachoSil; *Port.*: Evicel; TachoSil; Tissucol Duo†; *Rus.*: TachoComb (ТахоКомб); Tissucol Kit (Тиссукол Кит); *Singapore*: TachoComb; *Spain*: Artiss; Beriplast P Combi; Evicel; TachoSil; Tissucol Duo; *Swed.*: Artiss; Evicel; Quixil†; TachoSil; Tisseel Duo Quick; *Switz.*: Artiss; Beriplast P; Evicel; Quixil; TachoSil; Tisseel; Tissucol Duo S†; Tissucol†; *Thai.*: Fibingluraas; Tisseel; *Turk.*: Beriplast P; Tisseel VH; *UK*: TachoSil; Tisseel; *Ukr.*: TachoComb (ТахоКомб); *USA*: Artiss; Evarrest; Evicel; TachoSil; Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit; Human Fibrinogen.

Filgrastim *(BAN, USAN, rINN)*

Filgrastiimi; Filgrastimum; r-metHuG-CSF; XM-02 (filgrastim or tbo-filgrastim); Филграстим.

A recombinant human granulocyte colony-stimulating factor.
CAS — 121181-53-1.
ATC — L03AA02.
ATC Vet — QL03AA02.
UNII — PV15M0M1GW.

NOTE. The FDA approved the name tbo-filgrastim to describe the contents of *Granix (Teva, USA)*. However, in Europe this substance was granted marketing authorisation as a biosimilar filgrastim and marketed as *Tevagrastim (Teva, Europe)*.

Pharmacopoeias. In *US. Eur.* (see p. vii) includes a concentrated solution.

Ph. Eur. 8: (Filgrastim Concentrated Solution). A solution of a protein having the primary structure of the granulocyte colony-stimulating factor (G-CSF) plus 1 additional amino acid, an *N*-terminal methionine. In contrast to its natural counterpart, the protein is not glycosylated. It is produced by a method based on recombinant DNA technology, using bacteria as host cells. It contains a minimum 900 micrograms of protein per mL and has a minimum potency of 1.0×10^8 units per mg of protein. A clear, colourless, or slightly yellowish liquid.

USP 36: (Filgrastim). It is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains not less than 0.9 mg/mL of filgrastim. Store in airtight containers at a temperature between 2 degrees and 8 degrees. Protect from light during long-term storage.

Lipegfilgrastim *(USAN, rINN)*

Lipegfilgrastimum; XM-22; Липэгфилграстим.
Filgrastim conjugated with methoxy polyethylene glycol via a carbohydrate linker consisting of glycine, *N*-acetylneuraminic acid, and *N*-acetylgalactosamine.
CAS — 1117844-87-7.
ATC — L03AA14.
ATC Vet — QL03AA14.
UNII — 4AWF0N6QV3.

NOTE. The name Lonquex has been used as a trade mark for lipegfilgrastim.

Pegfilgrastim *(BAN, rINN)*

Pegfilgrastimi; Pegfilgrastimum; Pegfilgrastimun; Пегфильграстим.
Filgrastim conjugated with monomethoxy polyethylene glycol.
CAS — 208265-92-3.
ATC — L03AA13.
ATC Vet — QL03AA13.
UNII — 3A58010674.

Incompatibility. References.
1. Trissel LA, Martinez JF. Compatibility of filgrastim with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; 51: 1907–13.

Stability. Solutions of filgrastim must not be diluted with sodium chloride solutions as precipitation will occur. Glucose 5% solution may be used if dilution is necessary. However, filgrastim in diluted solution may be adsorbed onto glass or plastic materials and so it should not be diluted below the recommended minimum concentration (2 micrograms/mL). Also, to protect from adsorption, solutions that are diluted to concentrations of filgrastim below 15 micrograms/mL must have albumin added to give a final concentration of 2 mg/mL. For mention of the stability of filgrastim in a solution intended for enteral use in neonates, see Stability under Epoetins, p. 1141.2.

Uses and Administration

Filgrastim is a granulocyte colony-stimulating factor (G-CSF), a haematopoietic growth factor that stimulates the development of granulocytes (see Haematopoiesis, p. 1121.1). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation. It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation. Filgrastim is also used in the management of chronic neutropenia (congenital, cyclic, or idiopathic), and for persistent neutropenia in patients with advanced HIV infection.

Filgrastim may be given intravenously or subcutaneously. Doses may be expressed in micrograms or in units; 10 micrograms is equivalent to 1 million units.

As an **adjunct to antineoplastic therapy**, filgrastim is given in a dose of 5 micrograms/kg daily starting not less than 24 hours after the last dose of antineoplastic. It can be given as a single daily subcutaneous injection, as a continuous intravenous or subcutaneous infusion, or as a daily intravenous infusion over 15 to 30 minutes. Treatment is continued until the neutrophil count has stabilised within the normal range which may take up to 14 days or more. A formulation of filgrastim conjugated with monomethoxy polyethylene glycol (pegfilgrastim) may also be used to reduce the incidence of neutropenia associated with antineoplastic therapy; it is given by subcutaneous injection in a single dose of 6 mg, given not less than 24 hours after the last dose of antineoplastic. Lipegfilgrastim, described as a glycopegylated filgrastim, is also in development for this indication; a single dose of 6 mg is given subcutaneously about 24 hours after chemotherapy.

The initial dose of filgrastim following **bone marrow transplantation** is 10 micrograms/kg daily, adjusted according to response. This may be given by intravenous infusion over 30 minutes or 4 hours, or by continuous intravenous or subcutaneous infusion over 24 hours.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 10 micrograms/kg daily of filgrastim may be given subcutaneously as a single daily injection or by continuous infusion for 4 to 7 days until the last leucapheresis procedure (usually performed on days 5 to 7 as required). If filgrastim is given after myelosuppressive chemotherapy, the dose is halved to 5 micrograms/kg daily by subcutaneous injection. It is given from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, so that leucapheresis can be performed. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 4 or 5 days until leucapheresis (usually started on day 5).

In patients with **congenital neutropenia** the initial dose is 12 micrograms/kg daily and in patients with idiopathic or cyclic neutropenia the initial dose is 5 micrograms/kg daily. In these forms of neutropenia the dose is given subcutaneously in single or divided doses and should be adjusted according to response.

In patients with **HIV infection** and persistent neutropenia the initial dose is 1 microgram/kg daily by subcutaneous injection. The dose may be titrated up to a maximum of 4 micrograms/kg daily until a normal neutrophil count is achieved and then adjusted for maintenance according to response. Maintenance doses of 300 micrograms daily on 1 to 7 days a week have been used.

The filgrastim doses described above for patients receiving antineoplastic therapy and for chronic neutropenias may also be given to **children**. The use of pegfilgrastim in children is limited and its safety and efficacy have not been adequately established.

References and reviews.
1. Dale DC, ed. Filgrastim anniversary supplement: reviewing 10 years of clinical experience, a seminar-in-print. *Drugs* 2002; 62 (suppl 1): 1–98.
2. Curran MP, Goa KL. Pegfilgrastim. *Drugs* 2002; 62: 1207–13.
3. Renwick W, *et al.* Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs* 2009; 23: 175–86.
4. Bondarenko I, *et al.* Efficacy and safety of lipegfilgrastim versus pegfilgrastim: a randomized, multicenter, active-control phase 3 trial in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy. *BMC Cancer* 2013; 13: 386.

Aplastic anaemia. Colony-stimulating factors, including granulocyte colony-stimulating factors, have been tried in patients with aplastic anaemia (p. 1121.3).

Infections. As well as stimulating the development and maturation of haematopoietic precursors, granulocyte and granulocyte-macrophage colony-stimulating factors have been found to enhance neutrophil chemotaxis and phagocytosis, enhance oxidative activity, increase microbicidal activity and antibody-mediated cellular cytotoxicity, and delay neutrophil apoptosis. Granulocyte-macrophage colony-stimulating factor also modifies macrophage and monocyte functions in inflammation and cellular immune response.[1] It has therefore been suggested that colony-stimulating factors might be useful adjuncts in the treatment of infections in non-neutropenic patients, but their clinical role is yet to be established.

The use of granulocyte colony-stimulating factor was reported[2] to reduce mortality rates in patients with septic shock due to the bacterial infection melioidosis (p. 190.2). In small placebo-controlled studies of patients with the protozoal infection cutaneous leishmaniasis (p. 922.1), ulcers healed faster in those treated with granulocyte-macrophage colony-stimulating factor, as an adjunct to antimony therapy, by intralesional injection[3] and topical application.[4]

However, granulocyte colony-stimulating factor does not appear to be of benefit as an adjunct in the management of pneumonia[5] (p. 200.1). In diabetic foot infections (see Diabetic Foot Disease, p. 464.2) granulocyte colony-stimulating factor does not appear to affect wound healing, although there is some suggestion that it may reduce the likelihood of surgical intervention.[6]

In HIV infection (p. 957.2), granulocyte-macrophage colony-stimulating factor has been reported to improve CD4 + cell counts.[7]

Granulocyte-macrophage colony-stimulating factor has been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[8]

1. Root RK, Dale DC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in nonneutropenic patients. *J Infect Dis* 1999; 179 (suppl): S342–S352.
2. Cheng AC, *et al.* Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis* 2004; 38: 32–7.
3. Almeida R, *et al.* Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony-stimulating factor versus stibogluconate alone in the treatment of cutaneous leishmaniasis. *J Infect Dis* 1999; 180: 1735–7.
4. Santos JB, *et al.* Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. *J Infect Dis* 2004; 190: 1793–4.
5. Cheng AC, *et al.* Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 16/06/08).
6. Cruciani M, *et al.* Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care* 2005; 28: 454–60.
7. Deresinski SC. Granulocyte-macrophage colony-stimulating factor: potential therapeutic, immunological and antiretroviral effects in HIV infection. *AIDS* 1999; 13: 633–43.
8. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; 25: 709–18.

Ischaemia. Colony-stimulating factors have been investigated for their ability to mobilise stem cells and modulate inflammation in cardiovascular disorders characterised by ischaemia. Granulocyte colony-stimulating factor (G-CSF) has been tried in atherosclerotic coronary artery disease and particularly after myocardial infarction (p. 1257.1). However, studies have been small, and reviews have concluded that although there was mobilisation of stem cells that might be of benefit in myocardial regeneration, G-CSF provided no additional benefit to reperfusion therapy after myocardial infarction.[1,2] A systematic review also concluded that the use of G-CSF did not increase the risk of coronary restenosis or cardiovascular events after reperfusion therapy for myocardial infarction.[3] Benefit has been reported in 7 patients with acute ischaemic stroke (p. 1269.2) given filgrastim 15 micrograms/kg subcutaneously daily for 5 days in addition to the usual care given to 3 controls.[4] There was a greater improvement in neurological function in filgrastim-treated patients on 12 months of follow-up, but larger studies are required to confirm the benefit.

1. Kastrup J, *et al.* Myocardial regeneration induced by granulocyte-colony-stimulating factor mobilization of stem cells in patients with acute or chronic ischaemic heart disease: a non-invasive alternative for clinical stem cell therapy? *Eur Heart J* 2006; 27: 2748–54.
2. Zohlnhöfer D, *et al.* Stem cell mobilization by granulocyte colony-stimulating factor for myocardial recovery after acute myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 2008; 51: 1429–37.
3. Ince H, *et al.* Cardiovascular events and re-stenosis following administration of G-CSF in acute myocardial infarction: systematic review and meta-analysis. *Heart* 2008; 94: 610–16.
4. Shyu W-C, *et al.* Granulocyte colony-stimulating factor for acute ischemic stroke: a randomized controlled trial. *Can Med Assoc J* 2006; 174: 927–33.

Neutropenia. Granulocyte colony-stimulating factors are used in the management of neutropenia. They may be used[1] long-term in the management of inherited forms of neutropenia (p. 1130.1). They are used short-term[2–5] to treat or prevent antineoplastic-induced neutropenia (p. 731.1) and have also been used in patients with neutropenia induced by other drugs.[6–11] Colony-stimulating factors are also used[12] in the management of neutropenia in patients with HIV-associated infection (p. 958.3) including that due to myelosuppressive therapies such as cotrimoxazole, pyrimethamine, and zidovudine. A controlled study[13] in 258 patients with advanced HIV infection found that prophylactic use of granulocyte colony-stimulating factor reduced the incidence of severe neutropenia and also suggested that the incidence and duration of bacterial infections was reduced.

Due to immature neutrophil production and function, neonates are susceptible to infection and preterm neonates are at particular risk. The use of colony-stimulating factors for prophylaxis or as adjuncts in the treatment of septicaemia (p. 203.2) in neonates has been investigated in a few small studies but there is insufficient evidence of benefit to recommend the use of granulocyte or granulocyte-macrophage colony-stimulating factors in these patients. There is also limited evidence to suggest that they may reduce mortality as adjuncts to treatment in

patients with sepsis and severe neutropenia.[14,15] Granulocyte colony-stimulating factors have also been tried with mixed results in neonates with the rare condition of alloimmune neutropenia.[16,17]

1. Zeidler C, *et al.* Management of Kostmann syndrome in the G-CSF era. *Br J Haematol* 2000; **109**: 490–5.
2. Repetto L, *et al.* EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* 2003; **39**: 2264–72.
3. Sung L, *et al.* Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22**: 3350–6.
4. Clark OAC, *et al.* Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2005; **23**: 4198–4214.
5. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24**: 3187–3205. Also available at: http://jco.ascopubs.org/cgi/reprint/24/19/3187 (accessed 13/08/10)
6. Wickramanayake PD, *et al.* Use of granulocyte colony-stimulating factor (filgrastim) in the treatment of non-cytotoxic drug-induced agranulocytosis. *Eur J Med Res* 1995; **1**: 153–6.
7. Murphy PT, Casey MC. Sulphasalazine induced agranulocytosis revisited. *Ir Med J* 1998; **91**: 216.
8. Bhidayasiri R, *et al.* Correction of mesalazine-induced neutropenia with high dose G-CSF. *Am J Gastroenterol* 2000; **95**: 3321–2.
9. Andrès E, *et al.* Nonchemotherapy drug-induced agranulocytosis in elderly patients: the effects of granulocyte colony-stimulating factor. *Am J Med* 2002; **112**: 460–4.
10. Andrès E, *et al.* Modern management of non-chemotherapy drug-induced agranulocytosis: a monocentric cohort study of 90 cases and review of the literature. *Eur J Intern Med* 2002; **13**: 324–8.
11. Hägg S, *et al.* Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol* 2003; **18**: 173–4.
12. Kuritzkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin Infect Dis* 2000; **30**: 256–60.
13. Kuritzkes DP, *et al.* Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. *AIDS* 1998; **12**: 65–74.
14. Banerjea MC, Speer CP. The current role of colony-stimulating factors in prevention and treatment of neonatal sepsis. *Semin Neonatol* 2002; **7**: 335–49.
15. Carr R, *et al.* G-CSF and GM-CSF for treating or preventing neonatal infections. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 27/10/05).
16. Felix JK, Calhoun DA. Neonatal alloimmune neutropenia in premature monozygous twins. *Pediatrics* 2000; **106**: 340–2.
17. Maheshwari A, *et al.* Resistance to recombinant human granulocyte colony-stimulating factor in neonatal alloimmune neutropenia associated with anti-human neutrophil antigen-2a (NB1) antibodies. Abstract: *Pediatrics* 2002; **109**: 698. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/4/e64 (accessed 27/10/05)

Adverse Effects

The main adverse effects of granulocyte colony-stimulating factors such as filgrastim during short-term treatment are musculoskeletal pain and dysuria. Hypersensitivity reactions have been reported rarely. In patients receiving long-term treatment the most frequent adverse effects are bone pain and musculoskeletal pain. Other adverse effects include splenic enlargement, thrombocytopenia, anaemia, epistaxis, headache, diarrhoea, and cutaneous vasculitis. There have been reports of pulmonary infiltrates leading to respiratory failure or acute respiratory distress syndrome, and rare reports of splenic rupture. Rises in lactate dehydrogenase, alkaline phosphatase, and uric acid, are usually mild to moderate, dose-dependent, and reversible.

Colony-stimulating factors are fetotoxic in *animal* studies.

General references.

1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; **13**: 371–406.
2. Gutierrez-Delgado F, Bensinger W. Safety of granulocyte colony-stimulating factor in normal donors. *Curr Opin Hematol* 2001; **8**: 155–60.
3. Cottle TE, *et al.* Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. *Semin Hematol* 2002; **39**: 134–40.
4. Crawford J. Safety and efficacy of pegfilgrastim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2003; **23** (suppl): 15S–19S.
5. Pulsipher MA, *et al.* Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood* 2009; **113**: 3604–11.

Disseminated intravascular coagulation. Long-term treatment with granulocyte colony-stimulating factor in a 7-year-old boy with HIV infection and zidovudine-induced neutropenia produced evidence of disseminated intravascular coagulation on 2 occasions.[1]

1. Mueller BU, *et al.* Disseminated intravascular coagulation associated with granulocyte colony-stimulating factor therapy in a child with human immunodeficiency virus infection. *J Pediatr* 1995; **126**: 749–52.

Effects on the bones. Bone mineral loss and osteoporosis have been reported in children with severe congenital neutropenia receiving granulocyte colony-stimulating factor for long periods.[1-3] However, the role of granulocyte colony-stimulating factor in producing this effect is uncertain since bone mineral loss may be a feature of the underlying disease.

1. Bishop NJ, *et al.* Osteoporosis in severe congenital neutropenia treated with granulocyte colony-stimulating factor. *Br J Haematol* 1995; **89**: 927–8.
2. Yakisan E, *et al.* High incidence of significant bone loss in patients with severe congenital neutropenia (Kostmann's syndrome). *J Pediatr* 1997; **131**: 592–7.
3. Sekhar RV, *et al.* Severe osteopenia in a young boy with Kostmann's congenital neutropenia treated with granulocyte colony-stimulating factor: suggested therapeutic approach. Abstract: *Pediatrics* 2001; **108**: 756–7. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e54 (accessed 27/10/05)

Effects on the eyes. Subretinal haemorrhage resulting in irreversible loss of vision in one eye occurred in a 4-year-old girl who received filgrastim and nartograstim for chemotherapy-induced neutropenia and for mobilising peripheral blood stem cells.[1] It was postulated that the colony-stimulating factor reactivated a primary ocular inflammation probably caused by an infection. Bilateral peripapillary and macular retinal haemorrhage occurred in an adult being treated for mantle cell lymphoma.[2] It was attributed to retinal leucostasis secondary to hyperleucocytosis resulting from the use of filgrastim for stem cell mobilisation. Vision improved after cessation of filgrastim and the use of leucapheresis.

1. Matsumura T, *et al.* Subretinal haemorrhage after granulocyte colony-stimulating factor. *Lancet* 1997; **350**: 336. Correction. *ibid.*: 1406.
2. Salloum E, *et al.* Hyperleukocytosis and retinal hemorrhages after chemotherapy and filgrastim administration for peripheral blood progenitor cell mobilization. *Bone Marrow Transplant* 1998; **21**: 835–7.

Effects on the lungs. There have been reports of exacerbation of chemotherapy-induced pulmonary toxicity in patients receiving granulocyte colony-stimulating factor (G-CSF) with bleomycin, cyclophosphamide, or methotrexate. A systematic review[1] of 73 cases noted that the doses of the antineoplastics were below the usual toxic cumulative dose, suggesting that G-CSF may have lowered the threshold for pulmonary toxicity of these drugs. It has been proposed that G-CSF has an activating effect on neutrophils that makes them toxic to the alveolar capillary wall. The review also included 2 cases of pulmonary toxicity in non-neutropenic patients treated with G-CSF alone. The circumstances of 9 other cases suggested that neutropenic patients with a recent history of pulmonary infiltrates may be at increased risk of acute respiratory distress syndrome during neutropenia recovery. The true role of G-CSF in these cases of pulmonary toxicity remains unclear, however.

1. Azoulay E, *et al.* Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. *Chest* 2001; **120**: 1695–1701.

Effects on the skin. Skin reactions may occur in patients given colony-stimulating factors. In a study in women with inflammatory breast cancer, a pruritic skin reaction developed at the subcutaneous injection site in all 7 given granulocyte-macrophage colony-stimulating factor.[1] A review[2] of 8 cases of generalised pruritic maculopapular rash associated with granulocyte or granulocyte-macrophage colony-stimulating factor found that in 6 of them the rash resolved in 4 to 17 days even though therapy was continued and half the patients did not receive any treatment for the rash. A localised lichenoid reaction has been described for granulocyte colony-stimulating factor.[3] Exacerbation of psoriasis[4] and precipitation or exacerbation of neutrophilic dermatoses including Sweet's syndrome,[5-7] pyoderma gangrenosum,[8] and neutrophilic eccrine hidradenitis[9] have been reported following use of granulocyte colony-stimulating factor.

1. Steger GG, *et al.* Cutaneous reactions to GM-CSF in inflammatory breast cancer. *N Engl J Med* 1992; **327**: 286.
2. Álvarez-Ruiz S, *et al.* Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. *J Eur Acad Dermatol Venereol* 2004; **18**: 310–13.
3. Viallard AM, *et al.* Lichenoid cutaneous drug reaction at injection sites of granulocyte colony-stimulating factor (filgrastim). *Dermatology* 1999; **198**: 301–3.
4. Kavanaugh A. Flare of psoriasis and psoriatic arthritis following treatment with granulocyte colony-stimulating factor. *Am J Med* 1996; **101**: 567.
5. Petit T, *et al.* Lymphoedema-area-restricted Sweet syndrome during G-CSF treatment. *Lancet* 1996; **347**: 690.
6. Garty BZ, *et al.* Sweet syndrome associated with G-CSF treatment in a child with glycogen storage disease type Ib. *Pediatrics* 1996; **97**: 401–3.
7. Hasegawa M, *et al.* Sweet's syndrome associated with granulocyte colony-stimulating factor. *Eur J Dermatol* 1998; **8**: 503–5.
8. Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors: a review of associated neutrophilic dermatoses and vasculitides. *Arch Dermatol* 1994; **130**: 77–81.
9. Bachmeyer C, *et al.* Neutrophilic eccrine hidradenitis induced by granulocyte colony-stimulating factor. *Br J Dermatol* 1998; **139**: 354–5.

Effects on the thyroid. Reversible thyroid dysfunction has been reported in patients with pre-existing thyroid antibodies during treatment with granulocyte-macrophage colony-stimulating factor,[1] but not with granulocyte colony-stimulating factor.[2] However, clinical hypothyroidism has been reported in a patient with no history of thyroid dysfunction or thyroid antibodies during treatment with granulocyte colony-stimulating factor.[3]

1. Hoekman K, *et al.* Reversible thyroid dysfunction during treatment with GM-CSF. *Lancet* 1991; **338**: 541–2.
2. van Hoef MEHM, Howell A. Risk of thyroid dysfunction during treatment with G-CSF. *Lancet* 1992; **340**: 1169–70.
3. de Luis DA, Romero E. Reversible thyroid dysfunction with filgrastim. *Lancet* 1996; **348**: 1595–6.

Inflammatory disorders. Reactivation of various inflammatory disorders including rheumatoid arthritis[1] and pseudogout[2,3] has been reported after use of granulocyte colony-stimulating factors. For further reports of reactivation of sites of inflammation, see under Effects on the Eyes and Effects on the Skin, above.

1. Vildarsson B, *et al.* Reactivation of rheumatoid arthritis and development of leukocytoclastic vasculitis in a patient receiving granulocyte colony-stimulating factor for Felty's syndrome. *Am J Med* 1995; **98**: 589–91.
2. Sandor V, *et al.* Exacerbation of pseudogout by granulocyte colony-stimulating factor. *Ann Intern Med* 1996; **125**: 781.
3. Teramoto S, *et al.* Increased synovial interleukin-8 and interleukin-6 levels in pseudogout associated with granulocyte colony-stimulating factor. *Ann Intern Med* 1998; **129**: 424–5.

Precautions

Since granulocyte colony-stimulating factors such as filgrastim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although more recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. Filgrastim and lenograstim should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy because of the sensitivity of rapidly dividing myeloid cells. Pegfilgrastim should not be used from 14 days before until 24 hours after chemotherapy. The safety and efficacy of granulocyte colony-stimulating factor therapy has not been established in patients receiving chemoradiotherapy, and concomitant use is generally avoided.

Transient cytogenetic modifications have occurred in healthy donors given filgrastim for the mobilisation of peripheral blood progenitor cells. The significance of these changes is not known, and long-term safety follow-up of donors is ongoing. Until more is known, licensed product information recommends that donors should be monitored for at least 10 years.

Granulocyte colony-stimulating factors should be used with caution in patients with sickle-cell disease. Preparations of filgrastim may contain sorbitol as an excipient; care is advisable in patients with hereditary fructose intolerance.

The complete blood count should be monitored regularly during therapy with granulocyte colony-stimulating factors. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Transient positive changes in bone imaging findings have occurred with growth factor therapy, and should be considered when interpreting results. Bone density should be monitored in patients with osteoporosis who are receiving long-term treatment with filgrastim.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies filgrastim and pegfilgrastim as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Sickle-cell disease. Granulocytosis occurs during sickle-cell crisis (p. 1123.2) although the role of granulocytes in vaso-occlusion has not been established. Sickle-cell crisis has occurred in patients with sickle-cell disease who have been given granulocyte colony-stimulating factor.[1-3]

1. Abboud M, *et al.* Granulocytosis causing sickle-cell crisis. *Lancet* 1998; **351**: 959.
2. Adler BK, *et al.* Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. *Blood* 2001; **97**: 3313–14.
3. Wei A, Grigg A. Granulocyte colony-stimulating factor–induced sickle cell crisis and multiorgan dysfunction in a patient with compound heterozygous sickle cell/β⁺ thalassemia. *Blood* 2001; **97**: 3998–9.

Pharmacokinetics

After subcutaneous injection, peak serum concentrations of filgrastim occur within about 8 hours. The serum elimination half-life of filgrastim after intravenous or subcutaneous injection is about 3.5 hours. Pegfilgrastim peak concentrations occur later, at 16 to 120 hours after subcutaneous doses. Elimination of pegfilgrastim is non-linear and clearance becomes saturated and decreases with increasing dose. It is mainly eliminated by neutrophil-mediated clearance, such that the serum concentration of pegfilgrastim declines rapidly with neutrophil recovery. It has a half-life of 15 to 80 hours after subcutaneous injection.

Reviews.

1. Zamboni WC. Pharmacokinetics of pegfilgrastim. *Pharmacotherapy* 2003; **23** (suppl): 9S–14S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: FI-GCF; Filgen; Filgramega; Neulastim; Neupogen; Neutrofil; Neutromax; *Austral.*: Neulas-

The symbol † denotes a preparation no longer actively marketed

ta; Neupogen; Nivestim; Tevagrastim; ***Austria***: Neulasta; Neupogen; Nivestim; Ratiograstim; Zarzio; ***Belg.***: Neulasta; Neupogen; Tevagrastim; Zarzio; ***Braz.***: Filgrastine; Granulen; Granulokine; Leucin; Leukocim; Myograf; Neulastim; Tevagrastim; ***Canad.***: Neulasta; Neupogen; ***Chile***: Foltran; Neulastim; Neupogen; Neutromax; ***China***: Baolijin (保力津); Gran (惠尔血); Jilifen (吉粒芬); ***Cz.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Denm.***: Granulokine†; Neulasta; Neupogen; Nivestim; Ratiograstim†; Zarzio; ***Fin.***: Neulasta; Neupogen; ***Fr.***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Ger.***: Biograstim†; Neulasta; Neupogen; Nivestim; Ratiograstim; ***Gr.***: Granulokine; Neulasta; Nivestim; Tevagrastim†; Zarzio; ***Hong Kong***: Neulastim; Neupogen; Scimax; ***Hung.***: Neulasta; Neupogen; Ratiograstim; Tevagrastim; Zarzio; ***India***: Filgen; Grafeel; Grastim; Neukine; Neulastim; Neumax; Neupeg; Neupogen; NFil; Nufil-Safe; ***Indon.***: Leucogen; Leukokine; Neulastim; Neupogen; ***Irl.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Israel***: Neulastim; Neupogen; Tevagrastim; ***Ital.***: Granulokine; Neulasta; Neupogen†; Neupopeg†; Ratiograstim; ***Jpn***: Gran; ***Malaysia***: Gran; Neupogen; Peglasta; ***Mex.***: Biofilgran; Filatil; Inmunef†; Ior LC; Neukine; Neulastim; Neupogen; ***Neth.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Norw.***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***NZ***: Neulastim; Neupogen; ***Philipp.***: Granulokine; Macroleuco; Neulastyl; Peglasta; Recombicyte; SciLocyte; White-C; ***Pol.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Port.***: Biograstim; Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Rus.***: Filergim (Филергим); Granogen (Граноген); Grasalva (Грасальва); Leicita (Лейцита); Leucostim (Лейкостим); Mielastra (Миластра); Neitrostim (Нейтростим); Neulastim (Неуластим); Neupogen (Нейпоген); Neupomax (Нейпомакс); Tevagrastim (Теваграстим); ***S.Afr.***: Neupogen; ***Singapore***: Gran; Neulastim; Neupogen; Peglasta; ***Spain***: Neulasta; Neupogen; Nivestim; Ratiograstim; Zarzio; ***Swed.***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Switz.***: Neulasta; Neupogen; TevaGrastim; Zarzio; ***Thai.***: Filgen; Gran; Jilifen†; Neukine; Neulastim; Neupogen; Neutromax; Peglasta; ***Turk.***: Leucostim; Neupogen; ***UK***: Neulasta; Neupogen; Nivestim; Ratiograstim; Tevagrastim; Zarzio; ***Ukr.***: Filstim (Филстим); Grastim (Грастим); Neulastim (Неуластим); Neupogen (Нейпоген); TevaGrastim (ТеваГрастим); ***USA***: Granix; Neulasta; Neupogen; ***Venez.***: Neupogen.

Gelatin ⊗

Gelatina; Gelatine; Gélatine; Llivate; Modifiye Jelatin; Želatyna; Želatina; Zselatin; Желатин.

ATC — B02BC01 (absorbable gelatin sponge); B05AA06 (gelatin).

ATC Vet — QB02BC01 (absorbable gelatin sponge); QB05AA06 (gelatin).

UNII — 2G86QN327L

Grades. Gelling grades of gelatin are usually graded by gel strength, expressed as 'Bloom value', 'Bloom strength', or 'Bloom rating'.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.* Also in *USNF*.

The gelatin described in some pharmacopoeias is not necessarily suitable for preparations for parenteral use or for other special purposes.

Ph. Eur. 8: (Gelatin). A purified protein obtained either by partial acid hydrolysis (type A), by partial alkaline hydrolysis (type B), or by enzymatic hydrolysis of collagen from animals (including fish and poultry); it may also be a mixture of different types. The hydrolysis leads to gelling and non-gelling product grades. Gelling grades are characterised by the gel strength (Bloom value). It is not suitable for parenteral use or for other special purposes.

A faintly yellow or light yellowish-brown solid, usually occurring as translucent sheets, shreds, powder, or granules.

Gelling grades of gelatin swell in cold water and on heating give a colloidal solution which on subsequent cooling forms a more or less firm gel. Gelatin is practically insoluble in common organic solvents. Different gelatins form aqueous solutions that vary in clarity and colour. A 1% solution in water at about 55 degrees has a pH of 3.8 to 7.6. Protect from heat and moisture.

USNF 31: (Gelatin). It is obtained from collagen of animals (including fish and poultry) by partial alkaline and/or acid hydrolysis, by enzymatic hydrolysis, or by thermal hydrolysis. The hydrolysis leads to gelling or non-gelling grades.

Faintly yellow or amber sheets, flakes, or shreds, or a coarse to fine powder, the colour varying in depth according to the particle size. A solution has a slight, characteristic, bouillon-like odour. It is stable in air when dry, but is subject to microbial decomposition when moist or in solution. Gelatin swells and softens when immersed in cold water, gradually absorbing 5 to 10 times its weight of water. Soluble in hot water, in 6N acetic acid, and in a hot mixture of glycerol and water; insoluble in alcohol, in chloroform, in ether, and in fixed and volatile oils. Protect from heat and moisture.

Incompatibility. A white precipitate was formed immediately when vancomycin injection was infused through a giving set containing modified fluid gelatin solution.[1]

1. Taylor A, Hornbrey P. Incompatibility of vancomycin and gelatin plasma expanders. *Pharm J* 1991; **246**: 466.

Uses and Administration

Gelatin is a protein that has both clinical and pharmaceutical uses.

Gelatin is used as a haemostatic in surgical procedures as an absorbable film or sponge and can absorb many times its weight of blood. It is also employed as a plasma volume expander similarly to the dextrans in hypovolaemic shock (p. 1279.3). A 4% solution of a modified fluid gelatin (succinylated gelatin) has been infused in doses of 500 to 1000 mL. It may also be used in the form of a gelatin-derived polymer, see Polygeline, p. 1160.3.

Gelatin rods may be employed to temporarily block tear outflow in the diagnosis of dry eye (p. 2190.1).

Gelatin is used in the preparation of pastes, pastilles, suppositories, tablets, and hard and soft capsule shells. It is also used for the microencapsulation of drugs and other industrial materials. It has been used as a vehicle for injections: Pitkin's Menstruum, which consists of gelatin, glucose, and acetic acid, has been used in a modified form for heparin while hydrolysed gelatin has been used for corticotropin. Gelatin is an ingredient of preparations used for the protection of stomas and lesions.

Haemostasis. Gelatin acts as a haemostatic (p. 1124.3) by providing a physical meshwork within which clotting can occur.

Gelatin powder may be applied dry to wound beds and may be most useful when mixed with saline or thrombin and applied to bone. Gelatin sponge can be applied dry or soaked in saline or thrombin solutions. When applied to skin wounds the gelatin liquefies within 2 to 5 days; when implanted into tissues it is absorbed within 4 to 6 weeks. Adverse reactions include an increased incidence of infection, compression of surrounding tissue due to fluid absorption, granuloma formation, and fibrosis. Generally, gelatin sponges cause little tissue reaction and can be applied to bone, dura, and pleural tissue (but see also Hypersensitivity, below).

References.

1. Larson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; **14**: 623–32.
2. Schonauer C, *et al.* The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. *Eur Spine J* 2004; **13** (suppl): S89–S96.
3. Gabay M. Absorbable hemostatic agents. *Am J Health-Syst Pharm* 2006; **63**: 1244–53.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p. 1128.3). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155**: 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348**: 229–32.

Adverse Effects

Hypersensitivity reactions including anaphylactic reactions have occurred after the infusion of gelatin or its derivatives. Rapid infusion of gelatin derivatives may directly stimulate the release of histamine and other vasoactive substances.

For adverse reactions associated with the topical use of gelatin, see Haemostasis under Uses and Administration, above.

Hypersensitivity. Severe anaphylactoid reactions have been reported with infusion of modified fluid gelatin solutions.[1,2] As of June 2006, the Australian Adverse Drug Reactions Advisory Committee[3] had also received 70 reports of hypotension or hypersensitivity reactions associated with succinylated gelatin. Although severe hypersensitivity reactions to gelatin-based plasma expanders appear to be rare, they may be under-reported and fatalities have occurred.[2] The possibility of cross reactivity between succinylated gelatin and polygeline has also been considered; there are a few reports of patients who, after a reaction during clinical use with one plasma expander, have shown a positive skin test result to the other.[4,5] Some hypersensitivity reactions have been attributed to the use of gelatin as an excipient in vaccines[6-8] and other injectable drug products.[9] A haemostatic gelatin sponge put into place at the end of spinal surgery for a disc hernia was thought to be responsible for a delayed hypersensitivity reaction that caused oedema of the soft tissues and subsequent tingling and paresis of the lower limbs; removal of the sponge produced improvement.[10]

For reports of fatal reactions in asthmatic patients given gelatin derivatives, see Polygeline, p. 1160.3.

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4. Russell WJ, Fenwick DG. Anaphylaxis to Haemaccel and cross reactivity to Gelofusin. *Anaesth Intensive Care* 2002; **30**: 681–3.
5. Russell WJ, Fenwick DG. Cross-reactivity between Gelofusin and Haemaccel. *Anaesth Intensive Care* 2003; **31**: 121–2.
6. Kelso JM. The gelatin story. *J Allergy Clin Immunol* 1999; **103**: 200–202.
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8. Pool V, *et al.* Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. Abstract: *Pediatrics* 2002; **110**: 1241. Full version: http://pediatrics.aappublications.org/cgi/content/full/110/6/e71 (accessed 27/10/05)
9. Sakaguchi M, *et al.* A case of anaphylaxis to gelatin included in erythropoietin products. *J Allergy Clin Immunol* 1999; **103**: 349–50
10. Purello-D'Ambrosio F, *et al.* Allergy to gelatin. *Allergy* 2000; **55**: 414–15.

Precautions

When gelatin or its derivatives are used as plasma expanders the precautions under Dextran 70 (p. 1139.2) should be considered. There does not appear to be any interference with blood grouping and cross-matching of blood.

When gelatin is used as an absorbable haemostatic the precautions under Oxidised Cellulose (p. 1157.3) should be considered.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gelatin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

After infusion of modified fluid gelatin (succinylated gelatin), 75% of the dose is excreted in the urine in 24 hours. The half-life is about 4 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gelafundin; Geloplasma†; Infukoll; ***Austral.***: Gelfoam; Gelofusine; ***Austria***: Gelofusin; Geloplasma; ***Belg.***: Gelofusine; ***Braz.***: Colagenan†; Gelfoam; ***Canad.***: Gelfoam; ***Chile***: Gelfoam; Gelofusine; Geloplasma; ***China***: Gelofusine (佳乐施); Xue An (雪安); ***Cz.***: Gelofusine; Geloplasma; ***Denm.***: Gelofusine; ***Fin.***: Gelofusine; ***Fr.***: Bloxang†; Gel-Phan†; Gelodiet; Gelofusine; Plasmion; ***Ger.***: Gelafundin; Gelafusal; Gelaspon; Gelastypt; Spongostan; stypro; ***Gr.***: Gelofusine; ***Hong Kong***: Gelofusine; ***Hung.***: Gelofusine; ***India***: Seraccel; ***Indon.***: Gelafundin; ***Irl.***: Gelaspan; Gelofusine; Geloplasma; ***Israel***: Gelfoam†; ***Ital.***: Cutanplast†; Eufusin; Gelofusine; Infuplas; Spongostan; Surgiflo; ***Malaysia***: Gelfoam; ***Mex.***: Gelafundin; ***Neth.***: Gelaspan; Gelofusine; Geloplasma; ***Norw.***: Gelaspan; ***NZ***: Gelafusal; Gelfilm†; Gelfoam†; Gelofusine†; ***Philipp.***: Gelfoam; ***Pol.***: Gelofusine; Geloplasma; ***Port.***: Gelafundina†; Gelofusine; Geloplasma; ***Rus.***: Gelatinol (Желатинол); Gelofusin (Гелофузин); Geloplasma (Гелоплазма); ***S.Afr.***: Gelofusine; ***Singapore***: Gelfoam; Gelofusine; ***Spain***: Gelafundina; Geloplasma; ***Swed.***: Gelaspan; Gelofusine; ***Switz.***: Physiogel; ***Thai.***: Gelafundin†; Gelofusine; ***Turk.***: Gelofusin; ***UK***: Gelaspan; Gelofusine; Geloplasma; Isoplex; Volplex; ***Ukr.***: Gelofusine (Гелофузин); ***USA***: Gelfilm; Gelfoam; ***Venez.***: Gelfoam; Gelofusine.

Multi-ingredient Preparations. ***Arg.***: Aminoterapia; Cistimax; Megaplus; Mucobase; Valcatil Plus; Valcatil; ***Austral.***: Orabase; Stomahesive; ***Canad.***: Orabase; Orahesive; Tegasorb†; ***Fr.***: Rectopanbiline; ***Gr.***: Geloplasma; ***India***: Gelofusine; ***Indon.***: Nutrasendi; ***Irl.***: Orabase†; ***Ital.***: Eavit Plus; Eavit; Solecin†; Vitalux Plus; ***Jpn***: Choreito; Choreitogoshimotsuto; Kyukikyogaito; Shakanzoto; Unkeito; ***NZ***: Orabase; Stomahesive; ***Philipp.***: Thinber Fiber Complex†; ***Port.***: Dagragel; Efluvium Saquetas†; ***Rus.***: Gelplastan (Желпластан); ***S.Afr.***: Granuflex; Orabase†; ***Singapore***: Androlistica; ***UK***: Orabase; Orahesive; Stomahesive; ***USA***: Dome-Paste.

Pharmacopoeial Preparations

USP 36: Absorbable Gelatin Film; Absorbable Gelatin Sponge.

Haemoglobin ⊗

Emoglobina; Hämoglobin; Hemoglobiini; Hemoglobin; Hemoglobina; Hemoglobine; Hæmoglobin; Гемоглобин.

Hemoglobin Glutamer (rINN) ⊗

Haemoglobin Glutamer; Hemoglobina glutámero; Hémoglobine Glutamère; Hemoglobinum Glutamerum; Гемоглобин Глутамер.

ATC — B05AA10 (bovine).

ATC Vet — QB05AA10 (bovine); QB05AA90.

NOTE. The species of origin and average molecular mass should be indicated (e.g. hemoglobin glutamer-250 (bovine) indicates a polymerised haemoglobin of bovine origin with an average mass of 250 kD).

Profile

Haemoglobin has the property of reversible oxygenation and is the respiratory pigment of blood. Solutions of haemoglobin or modified haemoglobin are being investigated as blood substitutes.

Hemoglobin glutamer-250 (bovine) (HBOC-201; haemoglobin-based oxygen carrier-201) is a polymerised bovine haemoglobin that is used for the treatment of anaemia in surgical patients.

Hemoglobin glutamer-200 (bovine) (HBOC-301) is used in veterinary medicine for the treatment of anaemia in *dogs*.

Pyridoxalated haemoglobin polyoxyethylene (hemoximer) is reported to have nitric oxide scavenging effects. It is under investigation in shock.

Use. The structure of haemoglobin gives a non-linear oxygen dissociation curve; almost maximum oxygen saturation occurs in normal arterial blood without the need for oxygen-enriched air. Thus the use of haemoglobin solutions for emergencies appears logical. Initial *animal* experiments with haemoglobin from haemolysed erythrocytes resulted in serious renal damage but haemoglobin is not itself nephrotoxic and the development of stroma-free haemoglobin solutions reduced this toxicity. However, once released from the erythrocytes, haemoglobin loses its ability to hold 2,3-diphosphoglycerate, which is essential for the delivery of oxygen, and haemoglobin, being a small molecule, is rapidly excreted by the kidneys. Various methods have been tried to overcome these problems; formation of crosslinked haemoglobin restores the oxygen affinity to that of whole blood and conjugation, polymerisation, or microencapsulation in a lipid membrane extend the half-life. Although there is ongoing development of these preparations there are reservations concerning haemoglobin solutions as blood substitutes. Bovine blood is one source used for production but there are concerns about potential antigenicity or disease transmission; the use of outdated donated human blood is limited by availability. There is also concern about impairment of immune mechanisms. The development of recombinant human haemoglobin may overcome these problems and may allow further modification of the haemoglobin molecule.

References.
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2. Creteur J, Vincent J-L. Hemoglobin solutions. *Crit Care Med* 2003; **31** (suppl): S698–S707.
3. Chang TMS. Hemoglobin-based red blood cell substitutes. *Artif Organs* 2004; **28**: 789–94.
4. Mackenzie CF, Bucci C. Artificial oxygen carriers for trauma: myth or reality. *Hosp Med* 2004; **65**: 582–8.
5. Awasthi V. Pharmaceutical aspects of hemoglobin-based oxygen carriers. *Curr Drug Deliv* 2005; **2**: 133–42.
6. Stowell CP. What happened to blood substitutes? *Transfus Clin Biol* 2005; **12**: 374–9.
7. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; **11**: 4099–4114.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Hemopure.

Multi-ingredient Preparations. *Gr.*: Hemovital†; *India*: Globifex; Haem Up; Haem-Up Gems; HB Rich; Hemfast; Hemfer; Hepp Forte.

Human Haematopoietic Stem Cells

Stammzellen vom Menschen, Hämatopoetische.

Pharmacopoeias. In *Eur* (see p. vii).

Ph. Eur. 8: (Human Haematopoietic Stem Cells; Cellulae Stirpes Haematopoieticae Humanae). Primitive multipotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages. They are found in small numbers in bone marrow, in the mononuclear cell fraction of circulating blood and in umbilical cord blood. The preparation also contains haematopoietic progenitor cells, which are capable of differentiation but not self-renewal. The numbers of haematopoietic stem cells and haematopoietic progenitor cells are correlated.

Profile

Haematopoietic stem cells and progenitor cells are produced during haematopoiesis (p. 1121.1). They may be collected directly from bone marrow, from peripheral blood after mobilisation, or from umbilical cord blood. These preparations are used in haematopoietic stem cell transplantation (p. 1937.1).

Infusion-related reactions to haematopoietic stem cell preparations may be caused by excipients. Patients given allogeneic haematopoietic stem cells are at risk of graft-versus-host disease and should receive appropriate immunosuppressive therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Hemacord.

Interleukin-3

IL-3; Interleucina 3; Interleukina 3; Interleuquina 3; Интерлейкин 3.

UNII — A802907MI4.

Profile

Interleukin-3 is a cytokine that acts as a colony-stimulating factor. It is under investigation in the management of myelosuppression associated with cancer chemotherapy and after bone marrow transplantation. A fusion molecule with granulocyte-macrophage colony-stimulating factor, known as milodistim (PIXY-321), has also been investigated but results have been disappointing.

Lenograstim (BAN, USAN, rINN)

Lenograstiimi; Lénograstim; Lenograstimum; rG-CSF; Ленограстим.

A recombinant human granulocyte colony-stimulating factor.

CAS — 135968-09-1.

ATC — L03AA10.

ATC Vet — QL03AA10.

UNII — 6WS4C399GB.

Stability. Solutions of colony-stimulating factors may be adsorbed onto glass or plastic materials. Solutions of lenograstim should not be diluted below the minimum recommended concentration for the formulation used.

Uses and Administration

Lenograstim is a granulocyte colony-stimulating factor with actions and uses similar to those of filgrastim (p. 1152.1). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p. 731.1). It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation. Lenograstim is also used in the treatment of severe congenital neutropenia (p. 1130.1).

When used as an **adjunct to antineoplastic therapy** and after **bone marrow transplantation**, lenograstim may be given in a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily. In patients receiving antineoplastics it is given subcutaneously, and in post-transplant patients it is given by intravenous infusion over 30 minutes or by subcutaneous injection. Lenograstim is started not less than 24 hours after the last dose of antineoplastic or the infusion of bone marrow or peripheral blood stem-cells. Treatment is given until the expected nadir has passed and the neutrophil count has stabilised at a level at which treatment can be stopped; the maximum recommended treatment period is 28 consecutive days.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily may be given by subcutaneous injection. It is started within 1 to 5 days after completion of chemotherapy and given until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leucapheresis is performed when the post-nadir leucocyte count is rising or after assessment of CD34+ cells in the blood. When used alone, a lenograstim dose of 10 micrograms/kg (1.28 million international units/kg) daily is given subcutaneously for 4 to 6 days, with leucapheresis usually performed between days 5 and 7. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 5 or 6 days before leucapheresis.

In patients with severe **congenital neutropenia** the initial dose of lenograstim is 150 micrograms/m^2 (equivalent to 5 micrograms/kg) daily by subcutaneous injection. Neutrophil recovery should be assessed over 7 to 14 days, and the dose may need to be adjusted up to 20 micrograms/kg daily. Maintenance therapy should be adjusted according to response, and a reduced dose or alternate day dosing may be possible in some patients.

References.
1. Frampton JE, *et al.* Lenograstim: a review of its pharmacological properties and therapeutic efficacy in neutropenia and related clinical settings. *Drugs* 1995; **49**: 767–93.
2. Dunn CJ, Goa KL. Lenograstim: an update of its pharmacological properties and use in chemotherapy-induced neutropenia and related clinical settings. *Drugs* 2000; **59**: 681–717.
3. Martino M, *et al.* Harvesting peripheral blood progenitor cells from healthy donors: retrospective comparison of filgrastim and lenograstim. *J Clin Apher* 2005; **20**: 129–36.

Adverse Effects and Precautions

As for Filgrastim, p. 1153.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lenograstim as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lenobio; *Austral.*: Granocyte; *Austria*: Granocyte; *Belg.*: Granocyte; *Braz.*: Granocyte; *Chile*: Granocyte; *China*: Granocyte (格拉诺赛特); *Denm.*: Granocyte; *Fin.*: Granocyte; *Fr.*: Granocyte; *Ger.*: Granocyte; *Gr.*: Granocyte; *Hung.*: Granocyte; *India*: Granocyte; *Indon.*: Granocyte; *Irl.*: Granocyte; *Israel*: Granocyte; *Ital.*: Granocyte; Myelostim; *Jpn*: Neutrogin; *Malaysia*: Granocyte; *Neth.*: Granocyte; *Norw.*: Granocyte†; *NZ*: Granocyte; *Philipp.*: Granocyte; *Pol.*: Granocyte; *Port.*: Granocyte; *Rus.*: Granocyte (Гранотит); *S.Afr.*: Granocyte; *Singapore*: Granocyte; *Spain*: Euprotin†; Granocyte; *Swed.*: Granocyte; *Switz.*: Granocyte; *Thai.*: Granocyte; *Turk.*: Granocyte; *UK*: Granocyte; *Ukr.*: Granocyte (Гранотит); *Venez.*: Granocyte.

Leucocytes

Leucociti; Leucócitos; Leucocitos; Leucocyti; Leukocitak; Leukocyten; Leukocyter; Leukocyty; Leukosyytit; Leukozyten; Лейкоциты.

Description. Preparations of leucocytes contain granulocytes with a variable content of red blood cells, lymphocytes, and platelets. Depending on the method of collection they may also contain dextran or hetastarch.

Uses and Administration

Transfusion of leucocytes has been used in patients with severe granulocytopenia and infection which has not been controlled by treatment with appropriate antimicrobials. A dose of granulocyte concentrate typically transfused for adults contains about 1×10^{10} neutrophils. Hydrocortisone and chlorphenamine have been given intravenously before transfusion to reduce the severity of adverse reactions.

References.
1. Yeghen T, Devereux S. Granulocyte transfusion: a review. *Vox Sang* 2001; **81**: 87–92.
2. Hubel K, Engert A. Granulocyte transfusion therapy for treatment of infections after cytotoxic chemotherapy. *Onkologie* 2003; **26**: 73–9.
3. Briones MA, *et al.* Granulocyte transfusion: revisited. *Curr Hematol Rep* 2003; **2**: 522–7.
4. Elebute M, *et al.* Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion*. 4th ed. Chichester: Wiley-Blackwell, 2009: 22–6.

Adverse Effects and Precautions

Leucocyte transfusions may cause severe transfusion reactions and fever. As with other blood products, there is a risk of transmission of infection. Severe lung reactions, including fluid overload with pulmonary oedema, are a particular problem in patients with active pulmonary infections.

Red blood cell compatibility testing is necessary because of the content of red blood cells. Graft-versus-host disease may occur in immunosuppressed recipients, and can be avoided by irradiating the product before it is given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Immodin; *Ger.*: Leuko-Norm†.

Methoxy Polyethylene Glycol-Epoetin Beta ⊗

Pegserepoetin Alfa; Pegzerepoetin Alfa; R-744; Ro-50-3821; Метоксиполиэтиленгликоль Эпоэтин Бета.
1-165-Erythropoietin (human) monoamide with α-(3-carboxypropyl)-ω-methoxypoly(oxy-1,2-ethanediyl).
CAS — 677324-53-7.
ATC — B03XA03.
ATC Vet — QB03XA03.
UNII — LR3UXN0193.

Uses and Administration

Methoxy polyethylene glycol-epoetin beta is described as a continuous erythropoietin receptor activator (CERA), with similar properties to the epoetins (p. 1141.2) but a longer duration of action. It is used in the treatment of symptomatic anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p. 1123.1). A starting dose of 600 nanograms/kg is given once every 2 weeks as a single intravenous or subcutaneous injection. Alternatively, for patients who are not on dialysis, a starting dose of 1.2 micrograms/kg once every month by subcutaneous injection may be given. For patients being switched from another erythropoiesis-stimulating agent such as an epoetin or darbepoetin alfa, the starting dose of methoxy polyethylene glycol-epoetin beta should be based on previous doses of these agents; high starting doses may be appropriate in some patients. The dose may be adjusted by about 25%, at monthly intervals, so that the rate of rise of haemoglobin is between 1 and 2 g per 100 mL each month. When the target haemoglobin concentration of between 10 and 12 g per 100 mL has been achieved, a maintenance dose may be given once monthly; this is equal to twice the dose that had been given once every 2 weeks.

Methoxy polyethylene glycol-epoetin beta is also under investigation in the treatment of anaemia in patients with non-myeloid malignant disease receiving chemotherapy.

References.
1. Sulowicz W, *et al.* PROTOS Study Investigators. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol* 2007; **2**: 637–46.
2. Levin NW, *et al.* MAXIMA study investigators. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet* 2007; **370**: 1415–21.
3. Österborg A, *et al.* Phase II study of three dose levels of continuous erythropoietin receptor activator (C.E.R.A.) in anaemic patients with aggressive non-Hodgkin's lymphoma receiving combination chemotherapy. *Br J Haematol* 2007; **136**: 736–44.
4. Klinger M, *et al.* Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomized trial. *Am J Kidney Dis* 2007; **50**: 989–1000.
5. Spinowitz B, *et al.* RUBRA Study Investigators. C.E.R.A. maintains stable control of hemoglobin in patients with chronic kidney disease on dialysis when administered once every two weeks. *Am J Nephrol* 2008; **28**: 280–9.
6. Macdougall IC, *et al.* ARCTOS Study Investigators. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol* 2008; **3**: 337–47.
7. Canaud B, *et al.* STRIATA Study Investigators. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. *Nephrol Dial Transplant* 2008; **23**: 3654–61.
8. Curran MP, McCormack PL. Methoxy polyethylene glycol-epoetin beta: a review of its use in the management of anaemia associated with chronic kidney disease. *Drugs* 2008; **68**: 1139–56.

Adverse Effects and Precautions

As for Epoetins, p. 1143.3 and p. 1144.2.

Pharmacokinetics

In patients with chronic renal impairment, methoxy polyethylene glycol-epoetin beta is absorbed after subcutaneous injection with an absolute bioavailability of about 60%. It has a terminal elimination half-life of about 134 hours after intravenous injection and about 140 hours when given subcutaneously. Haemodialysis does not affect its pharmacokinetics.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mircera; ***Austral.***: Mircera; ***Belg.***: Mircera; ***Braz.***: Mircera; ***Chile***: Mircera; ***Cz.***: Mircera; ***Denm.***: Mircera; ***Fr.***: Mircera; ***Ger.***: Mircera; ***Gr.***: Mircera; ***Hong Kong***: Mircera; ***Hung.***: Mircera; ***India***: Mircera; ***Indon.***: Mircera; ***Irl.***: Mircera; ***Israel***: Mircera; ***Ital.***: Mircera; ***Jpn***: Mircera; ***Malaysia***: Mircera; ***Mex.***: Mircera; ***Neth.***: Mircera; ***Norw.***: Mircera; ***Philipp.***: Mircera; ***Pol.***: Mircera; ***Port.***: Mircera; ***Rus.***: Mircera (Мирцера); ***S.Afr.***: Mircera; ***Spain***: Mircera; ***Swed.***: Mircera; ***Switz.***: Mircera; ***Thai.***: Mircera; ***Turk.***: Mircera; ***UK***: Mircera; ***Ukr.***: Mircera (Мирцера).

Mirimostim *(rINN)*

Mirimostimum; Миримостим.
1–214-Colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced), homodimer.
CAS — 121547-04-4.

Profile

Mirimostim is a macrophage colony-stimulating factor (M-CSF). It promotes the differentiation and proliferation of monocytes and macrophage precursors, and stimulates secretion of granulocyte and granulocyte-macrophage colony-stimulating factors (see Haematopoiesis, p. 1121.1). Mirimostim is used in the management of neutropenia in patients receiving myelosuppressive cancer chemotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Leukoprol.

Molgramostim *(BAN, USAN, rINN)*

Molgramostiimi; Molgramostimum; Sch-39300; Молграмостим.
A recombinant human granulocyte-macrophage colony-stimulating factor; Colony-stimulating factor 2 (human clone pHG_{25} protein moiety reduced).
CAS — 99283-10-0.
ATC — L03AA03.
ATC Vet — QL03AA03.
UNII — B321AL142J.

Pharmacopoeias. *Eur.* (see p. vii) includes a concentrated solution.

Ph. Eur. 8: (Molgramostim Concentrated Solution; Molgramostimi Solutio Concentrata). A solution of a protein having the structure of the granulocyte-macrophage colony-stimulating factor which is produced and secreted by various human blood cell types. It contains not less than 2.0 mg of protein per mL. A clear, colourless liquid. Store in airtight containers at a temperature below -65 degrees. Protect from light.

Stability. Solutions of molgramostim may be adsorbed onto glass and plastic materials and therefore should not be diluted below the recommended minimum concentration of 7 micrograms/mL.

Uses and Administration

Molgramostim is a granulocyte-macrophage colony-stimulating factor (GM-CSF), a haematopoietic growth factor that stimulates the development of white blood cells, particularly granulocytes, macrophages, and monocytes (see Haematopoiesis, p. 1121.1). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p. 731.1). It has also been used to reduce ganciclovir-induced neutropenia (see Effects on the Blood, p. 983.3).

As an **adjunct to antineoplastic therapy**, molgramostim is given by subcutaneous injection, starting 24 hours after the last dose of antineoplastic, in a dose of 5 to 10 micrograms/kg (60 000 to 110 000 international units/kg) daily. Treatment should be continued for 7 to 10 days.

Following **bone marrow transplantation**, molgramostim may be given by intravenous infusion over 4 to 6 hours in a dose of 10 micrograms/kg (110 000 international units/kg) daily. Treatment should be begun the day after bone marrow transplantation and continued for up to 30 days depending on the neutrophil count.

For the management of **ganciclovir-induced neutropenia**, molgramostim has been given by subcutaneous injection in a dose of 5 micrograms/kg (60 000 international units/kg) daily. After 5 doses have been given the dose of molgramostim should be adjusted according to the neutrophil count.

The maximum dose for any indication should not exceed 10 micrograms/kg (110 000 international units/kg) daily.

General references.
1. Armitage JO. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1998; **92**: 4491–4508.
2. Mangi MH, Newland AC. Febrile neutropenia: prophylactic and therapeutic use of GM-CSF. *Eur J Cancer* 1999; **35** (suppl): S4–S7.
3. Croockewit S. GM-CSF in haematopoietic stem cell transplantation. *Eur J Cancer* 1999; **35** (suppl): S11–S13.
4. Sung L, *et al.* Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22**: 3350–6.
5. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24**: 3187–3205. Also available at: http://jco.ascopubs.org/cgi/reprint/24/19/3187 (accessed 13/08/10)

Infections. See under Filgrastim, p. 1152.2, and under HIV Infection and AIDS in Sargramostim, p. 1163.1.

Respiratory disorders. Pulmonary alveolar proteinosis is a rare diffuse lung disease that may result from impaired alveolar macrophage function caused by neutralising autoantibodies. It is characterised by excessive surfactant accumulation, and is usually managed with whole-lung lavage. Several months of therapy with subcutaneous granulocyte-macrophage colony-stimulating factor, typically in doses of 5 or 6 micrograms/kg daily, has been reported to induce remission in some patients.[1-7] Both molgramostim and sargramostim have been tried, but some reports are unclear as to which was used. There has also been a case report[8] of the effective use of inhaled granulocyte-macrophage colony-stimulating factor.

1. Barraclough RM, Gillies AJ. Pulmonary alveolar proteinosis: a complete response to GM-CSF therapy. *Thorax* 2001; **56**: 664–5.
2. Seymour JF, *et al.* Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. *Am J Respir Crit Care Med* 2001; **163**: 524–31.
3. Schoch OD, *et al.* BAL findings in a patient with pulmonary alveolar proteinosis successfully treated with GM-CSF. *Thorax* 2002; **57**: 277–80.
4. Romero A, *et al.* GM-CSF therapy in pulmonary alveolar proteinosis. *Thorax* 2002; **57**: 837.
5. Khanjari F, *et al.* GM-CSF and proteinosis. *Thorax* 2003; **58**: 645.
6. Abdul Rahman JA, *et al.* Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: successful treatment with granulocyte-macrophage colony stimulating factor after a partial response to whole lung lavage. *Respirology* 2004; **9**: 419–22.
7. Venkateshiah SB, *et al.* An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. *Chest* 2006; **130**: 227–37.
8. Arai T, *et al.* Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. *Respir Med* 2004; **98**: 1227–30.

Wounds and ulcers. Macrophages and granulocyte-macrophage colony-stimulating factors play important roles in several mechanisms essential to wound healing.[1] Recombinant granulocyte-macrophage colony-stimulating factors are being tried in non-healing wounds and ulcers (p. 1690.1), particularly chronic venous leg ulcers. They have been given by perilesional subcutaneous injection and topical application in a few small studies and case reports with apparent promotion of wound healing.[1] In a study[2] of patients with pressure ulcers, healing was better during a 35-day period of treatment with granulocyte-macrophage colony-stimulating factor compared with placebo. However, a year after the treatment period there was no difference.[3] In a group of 3 patients with inherited disorders of neutrophil function, topical sargramostim was reported to be of benefit in wound healing.[4] In 1 case sargramostim was also given by continuous subcutaneous infusion for 72 hours into the surgical site of a gastrostomy closure. Topical molgramostim has also been used to promote healing of sickle-cell leg ulcers.[5] Molgramostim has been used as a mouthwash to relieve severe recurrent aphthous mouth ulcers in a small number of patients with AIDS.[6] There has also been some investigation of the use of granulocyte-macrophage colony-stimulating factor for oral mucositis in cancer patients, particularly those undergoing radiotherapy for head and neck cancers. Small studies of subcutaneous injection or topical application as a mouthwash have provided some optimistic results.[7,8] Comparative studies, however, have found molgramostim to be no better than hydrocortisone mouthwash[9] and perhaps only slightly better than sucralfate mouthwash.[10]

1. Groves RW, Schmidt-Lucke JA. Recombinant human GM-CSF in the treatment of poorly healing wounds. *Adv Skin Wound Care* 2000; **13**: 10–12.
2. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231**: 600–611.
3. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181**: 81–6.
4. De Ugarte DA, *et al.* Treatment of chronic wounds by local delivery of granulocyte-macrophage colony-stimulating factor in patients with neutrophil dysfunction. *Pediatr Surg Int* 2002; **18**: 517–20.
5. Méry L, *et al.* Topical effectiveness of molgramostim (GM-CSF) in sickle cell leg ulcers. *Dermatology* 2004; **208**: 135–7.
6. Herranz P, *et al.* Successful treatment of aphthous ulcerations in AIDS patients using topical granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2000; **142**: 171–6.
7. Fung SM, Ferrill MJ. Granulocyte macrophage-colony stimulating factor and oral mucositis. *Ann Pharmacother* 2002; **36**: 517–20.
8. Mantovani G, *et al.* Phase II clinical trial of local use of GM-CSF for prevention and treatment of chemotherapy- and concomitant chemoradiotherapy-induced severe oral mucositis in advanced head and neck cancer patients: an evaluation of effectiveness, safety and costs. *Oncol Rep* 2003; **10**: 197–206.
9. Sprinzl GM, *et al.* Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. *Eur J Cancer* 2001; **37**: 2003–9.
10. Saarilahti K, *et al.* Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. *Int J Radiat Oncol Biol Phys* 2002; **54**: 479–85.

Adverse Effects

Granulocyte-macrophage colony-stimulating factors such as molgramostim may cause transient hypotension and

flushing, bone pain and musculoskeletal pain, fever and chills, dyspnoea, rash, fatigue, and gastrointestinal effects. Antibodies have been detected. Anaphylactic reactions, pleural and pericardial effusion, and cardiac arrhythmias have been reported rarely.

Colony-stimulating factors are fetotoxic in *animal* studies.

General references.
1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; 13: 371–406.
2. Moleski RJ. Comparison of G-CSF and GM-CSF adverse event profiles in office-based practices: preliminary study results. *Pharmacotherapy* 2000; 20 (suppl): 112S–117S.
3. Milkovich G, *et al.* Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2000; 20: 1432–40.

Antibodies. Antibodies can develop in patients given recombinant granulocyte-macrophage colony-stimulating factors. The antibodies have been reported to occur more commonly, and in higher titres, in patients who are not immunocompromised compared with those who are.[1,2] Although some binding antibodies are non-neutralising and have no apparent clinical effect,[3] neutralising antibodies can reduce the efficacy of the colony-stimulating factor in repeated treatment cycles.[1,2] However, antibodies have been reported to become undetectable after several weeks[2] and do not appear to have long-term effects.[1] Cross-reactivity between different granulocyte-macrophage colony-stimulating factors has been reported,[1-3] and antibody formation may also be product dependent.[2]

1. Ragnhammar P, *et al.* Induction of anti-recombinant human granulocyte-macrophage colony-stimulating factor (Escherichia coli-derived) antibodies and clinical effects in nonimmunocompromised patients. *Blood* 1994; 84: 4078–87.
2. Wadhwa M, *et al.* Immunogenicity of granulocyte-macrophage colony-stimulating factor (GM-CSF) products in patients undergoing combination therapy with GM-CSF. *Clin Cancer Res* 1999; 5: 1353–61.
3. Ulienhag G, *et al.* Incidence of GM-CSF antibodies in cancer patients receiving GM-CSF for immunostimulation. *Clin Immunol* 2001; 99: 65–74.

Effects on the skin. See under Filgrastim, p. 1153.2.

Effects on the thyroid. See under Filgrastim, p. 1153.2.

Precautions

Since granulocyte-macrophage colony-stimulating factors such as molgramostim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although more recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. They should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy or radiotherapy because of the sensitivity of rapidly dividing myeloid cells.

Granulocyte-macrophage colony-stimulating factors should be used with caution in patients with pulmonary disease as they may be predisposed to dyspnoea. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Caution is also necessary in patients with fluid retention or heart failure as fluid retention may be aggravated.

The complete blood count should be monitored regularly during therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies molgramostim as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Growgen-GM; Molcass; *Braz.*: Leucoclim; *Gr.*: Leucomax; Mielogen; *India*: Leucomax†; *Irl.*: Leucomax†; *Mex.*: Bagomol†; Gramal; *NZ*: Leucomax; *Rus.*: Neustim (Неостим); *Thai.*: Leucomax; *Turk.*: Leucomax.

Naftazone *(BAN, rINN)*

Naftazona; Naftazonum; Нафтазон.
1,2-Naphthoquinone 2-semicarbazone.
$C_{11}H_9N_3O_2$=215.2
CAS — 15687-37-3.
ATC — C05CX02.
ATC Vet — QC05CX02.
UNII — 15B0523PSL.

Profile

Naftazone is a haemostatic, and is reported to increase venous tone and have a capillary stabilising effect. It has been used in venous insufficiency of the lower limbs and diabetic retinopathy, in oral doses of 30 mg daily. It was formerly given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Mediaven; *Fr.*: Etioven; *Switz.*: Mediaven; *Turk.*: Mediaven.

Nartograstim *(rINN)*

Nartograstimum; Нартограстим.
A recombinant human granulocyte colony-stimulating factor; *N*-L-Methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine colony-stimulating factor (human clone 1034).
CAS — 134088-74-7.

Profile

Nartograstim is a granulocyte colony-stimulating factor with properties similar to those of filgrastim (p. 1151.3). It has been given by intravenous or subcutaneous injection in the management of neutropenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Neu-Up.

Oprelvekin *(USAN, rINN)*

Oprelvekina; Oprelvékine; Oprelvekinum; rhIL-11; YM-294; Опрельвекин.
2-178-interleukin 11 (human clone pXM/IL-11).
$C_{854}H_{1411}N_{253}O_{235}S_2$=19047.3
CAS — 145941-26-0.
ATC — L03AC02.
ATC Vet — QL03AC02.
UNII — HM5641GA6F.

Uses and Administration

Oprelvekin, a recombinant human interleukin-11, is a platelet growth factor that stimulates the proliferation and maturation of megakaryocytes and thus increases the production of platelets. Oprelvekin is given by subcutaneous injection in a dose of 50 micrograms/kg daily to prevent severe thrombocytopenia and reduce the need for platelet transfusions in high-risk patients after myelosuppressive, but not myeloablative, chemotherapy for non-myeloid malignancies (see Thrombocytopenia under Treatment of Adverse Effects in Antineoplastics, p. 731.2). The dose should be reduced in severe renal impairment (see below). The initial dose should be given 6 to 24 hours after the last dose of antineoplastic, and continued up to a maximum of 21 days. Treatment with oprelvekin should be stopped at least 2 days before starting the next planned cycle of chemotherapy.

Oprelvekin has been investigated for the treatment of Crohn's disease, rheumatoid arthritis, and chronic hepatitis C.

Administration in renal impairment. In severe renal impairment (creatinine clearance less than 30 mL/min) the recommended dose of oprelvekin is 25 micrograms/kg daily by subcutaneous injection.

Thrombocytopenia. References.

1. Tepler I, *et al.* A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood* 1996; 87: 3607–14.
2. Isaacs C, *et al.* Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *J Clin Oncol* 1997; 15: 3368–77.
3. Reynolds CH. Clinical efficacy of rhIL-11. *Oncology (Huntingt)* 2000; 14 (suppl 8): 32–40.

Adverse Effects and Precautions

Fluid retention may occur and lead to peripheral oedema, dyspnoea and pulmonary oedema, capillary leak syndrome, and exacerbation of pre-existing pleural effusions; caution is required when giving oprelvekin to patients with a history or signs of heart failure. Dilutional anaemia may occur. Fluid balance and electrolytes should be monitored in patients receiving long-term diuretic therapy. Transient atrial arrhythmias commonly occur; there have also been some reports of ventricular arrhythmias occurring within 2 to 7 days of starting oprelvekin. Other adverse effects include exfoliative dermatitis, blurred vision, and conjunctival injection. Hypersensitivity reactions, including anaphylaxis, have been reported with the use of oprelvekin. Papilloedema has been reported, and oprelvekin should be used with caution in patients with pre-existing papilloedema or tumours involving the CNS.

Use of oprelvekin after myeloablative chemotherapy and bone marrow transplantation is considered to be contra-indicated because of an increased incidence of adverse effects.

Fetotoxicity has been reported in *animals*.

Reviews.
1. Smith JW. Tolerability and side-effect profile of rhIL-11. *Oncology (Huntingt)* 2000; 14 (suppl 8): 41–7.

Effects on the eyes. Papilloedema has been reported in patients treated with oprelvekin,[1] and was found to be a dose-limiting adverse effect in a study of safety and pharmacokinetics in children.[2]

1. Peterson DC, *et al.* Oprelvekin-associated bilateral optic disk edema. *Am J Ophthalmol* 2005; 139: 367–8.
2. Cairo MS, *et al.* Phase I/II dose escalation study of recombinant human interleukin-11 following ifosfamide, carboplatin and etoposide in children, adolescents and young adults with solid tumours or lymphoma: a clinical, haematological and biological study. *Br J Haematol* 2005; 128: 49–58.

Pharmacokinetics

The bioavailability of oprelvekin after subcutaneous injection is about 80%, peak serum concentrations occur after about 3 hours, and it has a terminal half-life of about 7 hours. Oprelvekin is metabolised before excretion by the kidneys, and its clearance is reduced in renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Neumega; Plaquemax; *China*: Jijufen (吉巨芬); *Israel*: Neumega†; *Rus.*: Neumega (Ньюмега); *USA*: Neumega; *Venez.*: Neumega.

Oxidised Cellulose

Ácido celulósico; Cellulosic Acid; Celulosa oxidada; Oxidized Cellulose; Целлюлоза Окисленная.
CAS — 9032-53-5.
ATC — B02BC02.
ATC Vet — QB02BC02.

Description. Oxidised cellulose is a sterile polyanhydroglucuronic acid, prepared by the oxidation of a suitable form of cellulose.

Pharmacopoeias. In *US* which also includes Oxidized Regenerated Cellulose.

USP 36: (Oxidized Cellulose). It contains not less than 16% and not more than 24% of carboxyl groups, calculated on the dried basis. It is a slightly off-white gauze or lint with a slight, charred odour. Insoluble in water and in acids; soluble in dilute alkalis. Store at a temperature not exceeding 8 degrees. Protect from direct sunlight.

USP 36: (Oxidized Regenerated Cellulose). It contains 18 to 24% of carboxyl groups calculated on the dried basis. It is a slightly off-white knit fabric, with a slight odour. Insoluble in water and in dilute acids; soluble in dilute alkalis. Store at a temperature between 15 degrees and 30 degrees. Protect from direct sunlight.

Uses and Administration

Oxidised cellulose and oxidised regenerated cellulose are absorbable haemostatics (p. 1124.3). When applied to a bleeding surface, they swell to form a gelatinous mass which aids in the formation of a clot. It is gradually absorbed by the tissues, usually within 7 to 14 days. These materials also have a weak bactericidal action. They are used in surgery as adjuncts in the control of moderate bleeding where suturing or ligation is impracticable or ineffective; they should not be used to control haemorrhage from large arteries. The gauze, lint, or knitted material should be laid on the bleeding surface or held firmly against the tissues until haemostasis is achieved; removal should then be considered (see Adverse Effects and Precautions, below). Oxidised cellulose should be used as the dry material as moistening will reduce its ability to absorb blood.

Adverse Effects and Precautions

Foreign body reactions may occur after the use of oxidised cellulose or oxidised regenerated cellulose. Headache, burning, and stinging have been reported and sneezing has been noted after use in epistaxis. Oxidised cellulose swells on contact with a bleeding surface; this could result in tissue necrosis, nerve damage, obstruction, or vascular stenosis if packed closely, especially into bony cavities, or if wrapped tightly around blood vessels. To minimise such complica-

tions the removal of excess material should be considered after haemostasis is achieved, and oxidised cellulose should always be removed after use near the spinal cord or optic nerve. Oxidised cellulose should not be used in packing or implantation for fractures since it may interfere with bone regeneration or cause cyst formation. It should not be used as a surface dressing, except for immediate control of haemorrhage, as it inhibits epithelialisation.

Oxidised cellulose should be used as the dry material since moistening will reduce its ability to absorb blood. Silver nitrate or other escharotic chemicals should not be applied before use as cauterisation might inhibit absorption of oxidised cellulose. Thrombin is inactivated by the low pH of oxidised cellulose; it is recommended that oxidised cellulose should not be impregnated with other haemostatics or antibacterials.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Surgicel†; *Ger.*: Tabotamp; *Hong Kong*: Stop Bleed; *Irl.*: Seal-On†; Traumacel P†; *Ital.*: Tabotamp; *UK*: Oxycel; StopBleed; *USA*: Oxycel; Surgicel.

Multi-ingredient Preparations. *Ital.*: Promogran Prisma; Promogran; *UK*: Seal-On.

Oxypolygelatin ⊗

Oxipoligelatina.

Profile

Oxypolygelatin is a polymer derived from gelatin (p. 1154.1). It has been used as a 5.5% solution as a plasma volume expander. There have been reports of anaphylaxis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Thai.*: Gelifundol†.

Peginesatide *(USAN, rINN)* ⊗

AF-37702 (peginesatide or peginesatide acetate); Peginesatida; Péginésatide; Peginesatidum; Пегинесатид.

$N^{\varepsilon 21},N^{\varepsilon 21'}$-{[($N^2$,$N^6$-bis{[ω-Methoxypoly(oxyethylene)]carbonyl}-D-lysyl-β-alanyl)imino]bis(methylenecarbonyl)}bis[acetylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(naphthalen-1-yl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminyl-L-prolyl-L-leucyl-L-arginyl-*N*-methylglycyl-L-lysinamide] cyclic (6→15:6'→15')-bisdisulfide.

$C_{231}H_{350}N_{62}O_{58}S_6(C_2H_4O)_n$

CAS — 913976-27-9; 1350810-60-4.

ATC — B03XA04.

ATC Vet — QB03XA04.

UNII — JX56W9N61Q.

NOTE. The name Hematide has been used as a trade mark for peginesatide.

Peginesatide Acetate *(USAN, rINNM)* ⊗

Acetato de peginesatida; AF-37702 (peginesatide or peginesatide acetate); Péginésatide, Acétate de; Peginesatidi Acetas; Пегинесатида Ацетат.

$C_{231}H_{350}N_{62}O_{58}S_6(C_2H_4O)_nxC_2H_4O$

CAS — 1185870-58-9; 1350810-83-1.

ATC — B03XA04.

ATC Vet — QB03XA04.

UNII — 44STTZ20CW.

Uses and Administration

Peginesatide is a synthetic pegylated peptide-based erythropoiesis-stimulating agent; it has no amino acid sequence homology with endogenous erythropoietin. It is used for the treatment of anaemia due to chronic kidney disease (see Normocytic-normochromic Anaemia, p. 1123.1) in patients on dialysis (but see Adverse Effects and Precautions, below). For an outline of blood cell formation in general and average cell counts in adults see Haematopoiesis, p. 1121.1. Peginesatide is given as the acetate although doses are expressed in terms of the base.

The aim of treatment is to use the lowest dose necessary to reduce the need for blood transfusion. Peginesatide may be started in patients with a haemoglobin concentration of less than 10 g per 100 mL; the dose should be reduced or therapy stopped when the concentration approaches or exceeds 11 g per 100 mL (for details see Haematocrit and Haemoglobin, under Precautions of Epoetins, p. 1144.3). The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension and the dose should be reduced if it exceeds 1 g per 100 mL in any 2-week period, or 2 g per 100 mL per month. The recommended initial dose of peginesatide for those who are not currently receiving erythropoiesis-stimulating agents is 40 micrograms/kg as an intravenous or subcutaneous injection given once monthly. In patients who have previously received such agents, the initial monthly dose of peginesatide should be based on the weekly dose of the erythropoiesis-stimulating agent at the time of switching. The dose may be increased at intervals of not less than 4 weeks, according to response, until the target haemoglobin concentration is achieved. Haemoglobin concentrations should be monitored at least every 2 weeks until stable, then at least monthly. In general, adjustments are made by increasing or decreasing the dose by about 25%. Treatment should be stopped if the response is inadequate after a 12-week escalation period.

References.

1. Stead RB, *et al.* Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. *Blood* 2006; **108**: 1830–4.
2. Macdougall IC. Hematide, a novel peptide-based erythropoiesis-stimulating agent for the treatment of anemia. *Curr Opin Investig Drugs* 2008; **9**: 1034–47.
3. Macdougall IC, *et al.* A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N Engl J Med* 2009; **361**: 1848–55.
4. Macdougall IC, *et al.* Dose-finding study of peginesatide for anemia correction in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2011; **6**: 2579–86.
5. Mikhail A. Profile of peginesatide and its potential for the treatment of anemia in adults with chronic kidney disease who are on dialysis. *J Blood Med* 2012; **3**: 25–31.
6. Graul AI. Peginesatide for the treatment of anemia in the nephrology setting. *Drugs Today* 2012; **48**: 395–403.

Adverse Effects and Precautions

As for Epoetins, p. 1143.3 and p. 1144.2. Serious, and sometimes fatal, hypersensitivity reactions have been reported with peginesatide; these have occurred within 30 minutes following its first intravenous use. In February 2013 the FDA instructed dialysis organisations to discontinue use of peginesatide pending investigation.

Pharmacokinetics

After subcutaneous injection, maximum plasma concentrations of peginesatide are reached in about 48 hours, and the bioavailability is about 46%. The mean half-life of peginesatide in healthy subjects is about 25 hours after intravenous injection and about 53 hours after subcutaneous injection. The mean half-life after intravenous use in dialysis patients is about 48 hours, and mean volume of distribution is about 35 mL/kg. Peginesatide is not metabolised and is excreted mainly in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Omontys.

Plasma

Blodplasma; Bloedplasma; Blutplasma; Osocze krwi; Plasma sanguíneo; Veriplasma; Плазма Крови.

ATC — B05AX03.

ATC Vet — QB05AX03.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p. vii).

Ph. Eur. 8: (Human Plasma for Fractionation; Plasma Humanum ad Separationem). The liquid part of human blood remaining after separation of the cellular elements from whole blood or collected in an apheresis procedure; it is intended for the manufacture of plasma-derived products. It is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

A light yellow to green, clear or slightly turbid liquid, without visible signs of haemolysis. Frozen plasma should be stored at or below -20 degrees; it may still be used for fractionation if the temperature is between -20 degrees and -15 degrees for not more than a total of 72 hours without exceeding -15 degrees on more than one occasion as long as the temperature is at all times -5 degrees or lower.

Ph. Eur. 8: (Human Plasma (Pooled and Treated for Virus Inactivation); Plasma Humanum Coagumentum Conditumque ad Exstinguendum Virum). A frozen or freeze-dried, sterile, non-pyrogenic preparation obtained from human plasma derived from donors belonging to the same ABO blood group. The plasma used complies with the requirements for Human Plasma for Fractionation (above). The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to inactivate known agents of infection.

The frozen preparation, after thawing, is a clear or slightly opalescent liquid free from solid and gelatinous particles. The freeze-dried preparation is an almost white or slightly yellow powder or friable solid.

Uses and Administration

Fresh frozen plasma contains useful amounts of clotting factors. It should be reserved for patients with proven abnormalities in blood coagulation. Indications include congenital deficiencies in clotting factors for which specific concentrates are unavailable, severe multiple clotting factor deficiencies (for example in patients with liver disease), rapid reversal of the action of coumarin anticoagulants, and disseminated intravascular coagulation. It may be used after massive blood transfusion when there is evidence of coagulation deficiency but its value for routine prophylaxis against abnormal bleeding tendencies in patients receiving massive blood transfusions is contentious except where clotting abnormalities have been confirmed. It has also been used in the treatment of thrombotic thrombocytopenic purpura and as a source of plasma proteins.

The amount of fresh frozen plasma transfused depends on the required level of clotting factors. A unit of fresh frozen plasma refers to the quantity of plasma obtained from 1 unit of whole blood; this generally represents a volume of about 250 mL, including anticoagulant.

Fresh frozen plasma should not be used as a volume expander or as a nutritional source.

Therapeutic plasma exchange or plasmapheresis (see below) are used in a wide variety of disorders.

Plasma is used to prepare blood products including albumin, antithrombin III, blood clotting factors, immunoglobulins, and platelets. Other preparations include cryoprecipitate depleted plasma, which is deficient in fibrinogen, factor VIII, von Willebrand factor, cryoglobulin, and fibronectin, and single donor plasma, which is not frozen. A solvent-detergent-treated plasma preparation is available.

Guidelines and reviews. General references to the use of plasma.

1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271**: 777–81.
2. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; **126**: 11–28. Also available at: http://www.bcshguidelines.com/pdf/freshfrozen_280604.pdf (accessed 27/10/05) Addenda, amendments, and corrections (4 sets) at http://www.bcshguidelines.com/pdf/Amendments_FFP_091205.pdf (issued 07/12/05),*ibid.* 2007; **136**: 514–16, at http://www.bcshguidelines.com/pdf/FFPAmendment_1_17_Oct_2007.pdf (issued 17/10/07), at http://www.bcshguidelines.com/pdf/FFPAmendment_2_17_Oct_2007.pdf (issued 17/10/07) (accessed 19/06/08)
3. Stanworth SJ, *et al.* Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; **126**: 139–52.
4. Cohen H, Baglin T. Plasma products and indications for their use. In: Contreras M, ed. *ABC of transfusion*. 4th ed. Chichester: Wiley-Blackwell, 2009: 40–47.

Hereditary angioedema. For a mention of fresh frozen plasma being used in hereditary angioedema, see p. 2485.2.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p. 1128.3). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155**: 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348**: 229–32.

Plasma exchange. Therapeutic plasma exchange or plasmapheresis are procedures in which plasma is selectively removed from the body while the cellular constituents of blood are retained. Although the two terms are commonly used synonymously, plasmapheresis generally involves the removal of small volumes of plasma, whereas plasma exchange removes larger volumes which must be replaced with a suitable fluid.

They have been tried in a number of disorders, including many with an immunological basis, when conventional treatment has not been successful. The aim is removal or reduction of those constituents of plasma causing or aggravating a disease or replacement of deficient plasma factors if the deficiency is the cause of the disorder.

Volume and frequency of plasma exchange is determined by the pathophysiology of the undesirable plasma constituent. For example, removal of antibody usually requires exchange of 1.5 times the estimated plasma volume

(3 to 4 litres) repeated daily or on alternate days until the desired reduction is obtained. The replacement fluid used depends on the volume and the condition being treated; albumin solutions, plasma expanders, or sodium chloride 0.9% are frequently used, whereas in conditions where there is deficiency of a plasma factor replacement of blood components such as immunoglobulins may be required. Fresh frozen plasma has been used as a replacement fluid but is associated with a high incidence of adverse effects and is generally reserved for the management of thrombotic thrombocytopenic purpura.

Technological developments, such as the use of specific adsorbents and the use of multiple filters with different pore sizes, may enable removal of only the desired constituent and avoid removal and subsequent replacement of total plasma.

References.
1. Michaud D, *et al.* Therapeutic plasma exchange. *Dynamics* 2001; **12:** 18–24.
2. Madore F. Plasmapheresis: technical aspects and indications. *Crit Care Clin* 2002; **18:** 375–92.
3. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; **19:** 157–67.

Thrombotic microangiopathies. Thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome are both syndromes characterised by intravascular platelet clumping.[1-6] Thrombocytopenia also occurs and fragmentation of erythrocytes, partly caused by the red cells passing through areas of the microvasculature occluded by the platelet aggregation, leads to microvascular haemolytic anaemia. In **thrombotic thrombocytopenic purpura** (TTP) the platelet aggregation is extensive and obstructs the vessels of various organs producing ischaemia or even infarction. The CNS, notably the brain, is often the area mainly affected although some degree of renal involvement may occur. It is an uncommon disorder; adult women, in whom the condition presents as a chronic relapsing illness, are slightly more frequently affected. It may be associated with abnormalities of von Willebrand factor due to deficiency or impaired activity of a protease, ADAMTS-13,[3,6] a recombinant form of which is under investigation for treatment.

In **haemolytic-uraemic syndrome** (HUS) the platelet aggregation is relatively less widespread and less severe and mainly affects the renal microvasculature although extrarenal manifestations may also occur. The primary consequences are hypertension and acute renal insufficiency or ultimately, if untreated, renal failure. Most cases of HUS occur in early childhood and follow a diarrhoeal illness caused by *Shigella dysenteriae* or *Escherichia coli*. However, the condition is becoming increasingly recognised in adults, particularly the elderly. Some cases may be drug induced. With appropriate symptomatic therapy HUS is typically a self-limiting disease with spontaneous recovery although fatalities have been known. Atypical HUS[7] is a rare form of disordered complement regulation often associated with genetic mutations; the prognosis for these patients is poor.

The supportive **management** of both syndromes follows similar lines.[1,3,4] In HUS, or TTP with renal symptoms, special attention needs to be directed towards the prevention of renal failure. Hypovolaemia should be corrected, with careful control of fluid and electrolyte balance and hypertension. Haemodialysis will be needed if renal failure develops. Severe anaemia requires blood transfusion, but platelet transfusion should be avoided.

Plasma exchange (see p. 1158.3) is considered to be the mainstay of therapy for TTP.[1-6] The optimal regimen has not been determined, but it is usually performed daily. There is also some debate about the preferred fluid replacement; plasma exchange using cryosupernatant (the plasma remaining after cryoprecipitate is prepared, and which is depleted of von Willebrand factor) may be more efficacious than fresh frozen plasma.[3] When plasma exchange is not available, infusion of fresh frozen plasma may be used.[1,3] In HUS, there is some debate over the use of plasma exchange or infusion. Some consider that these have no proven benefit in HUS[2,3] but others[1] have challenged this belief. Plasma exchange or infusion are also used in atypical HUS, although evidence for which is most appropriate is limited.[7]

Antiplatelet therapy and corticosteroids are often given, although neither has been adequately investigated and antiplatelets such as ticlopidine and clopidogrel have been reported to cause TTP (see p. 1512.3). Aspirin and dipyridamole have been used, but are not recommended when profound thrombocytopenia is present because of the potential bleeding risk, without proven benefit. However, low-dose aspirin may be used when platelet counts have recovered after plasma exchange in TTP.[1,3] Some reports have described improved outcome in both syndromes with corticosteroids.[8] They are often used with plasma exchange in TTP.[1,3,4] However, a randomised, double-blind study[9] in children with HUS failed to show any difference between oral corticosteroids and placebo in terms of haematological or neurological recovery, although renal function appeared to improve more rapidly in those receiving corticosteroids. Eculizumab, a complement pathway blocker, may be used in atypical HUS.[10]

Other drugs may also be tried, particularly in refractory TTP. Some treatments that have been reported to be beneficial in case reports or small series include normal immunoglobulin,[1,4] azathioprine,[1] ciclosporin,[1,3] cyclophosphamide,[3] and vincristine.[1-4] The monoclonal antibody, rituximab, has also been investigated.[2] The use of a protein-A immuno-adsorption column may be considered in the management of TTP associated with malignancy or bone marrow transplantation.[3] Epoprostenol may be tried in order to inhibit platelet-endothelial interactions but again has not been subject to controlled studies; anecdotal evidence presents both favourable and negative results.[11] Alteplase has been used successfully in one patient with HUS.[12] Splenectomy may also be considered.[1,3,4]

1. Elliott MA, Nichols WL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Mayo Clin Proc* 2001; **76:** 1154–62.
2. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; **347:** 589–600.
3. British Society for Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003; **120:** 556–73.
4. Nabhan C, Kwaan HC. Current concepts in the diagnosis and management of thrombotic thrombocytopenic purpura. *Hematol Oncol Clin North Am* 2003; **17:** 177–99.
5. Mayer SA, Aledort LM. Thrombotic microangiopathy: differential diagnosis, pathophysiology and therapeutic strategies. *Mt Sinai J Med* 2005; **72:** 166–75.
6. George JN. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006; **354:** 1927–35.
7. Taylor CM, *et al.* Working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. *Br J Haematol* 2010; **148:** 37–47.
8. Bell WR, *et al.* Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med* 1991; **325:** 398–403.
9. Perez N, *et al.* Steroids in the hemolytic uremic syndrome. *Pediatr Nephrol* 1998; **12:** 101–4.
10. Hodgkins KS, *et al.* Clinical grand rounds: atypical hemolytic uremic syndrome. *Am J Nephrol* 2012; **35:** 394–400.
11. Bobbio-Pallavicini E, *et al.* Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79:** 429–37.
12. Kruez W, *et al.* Successful treatment of haemolytic-uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; **341:** 1665–6.

Adverse Effects and Precautions

As for Blood, p. 1135.3, though with a low risk of transmitting cell-associated viruses. However, the production of blood products using plasma from UK donors has been phased out due to the possible risk of transmission of variant Creutzfeldt-Jakob disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Octaplas; *Belg.*: Octaplas; *Cz.*: Octaplas; *Fin.*: Octaplas; *Ger.*: Octaplas; *Hung.*: Octaplas; *Irl.*: Octaplas; *Ital.*: Octaplas; Plasmasafe; *Mex.*: Octaplas; *Neth.*: Octaplas†; Omniplasma; *Norw.*: Octaplas; *NZ*: Octaplas; *Port.*: Novoplas; Octaplas; *Swed.*: Octaplas; *Switz.*: Octaplas; *UK*: Octaplas; *USA*: Octaplas.

Multi-ingredient Preparations. *Port.*: Quixil†; *Rus.*: Gelplastan (Гелпластан).

Plasma Protein Fraction ⊗

Fracción proteica del plasma; Белковые Фракции Плазмы.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US*.

USP 36: (Plasma Protein Fraction). A sterile preparation of serum albumin and globulin obtained by fractionating material (blood, plasma, or serum) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It contains 5% of protein; not less than 83% of the total protein is albumin; not more than 17% is alpha and beta globulins; not more than 1% has the electrophoretic properties of gamma globulin. It contains sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent but no antimicrobial preservative. It contains 130 to 160 mmol/litre of sodium, and not more than 2 mmol/litre of potassium. A solution in 0.15M sodium chloride containing 1% protein has a pH between 6.7 and 7.3. It should be used within 4 hours of opening the container.

Profile

Plasma protein fraction consists mainly of albumin with a small proportion of globulins; it does not contain blood-clotting factors. It has properties and uses similar to those of other albumin solutions (p. 1130.3). It is given intravenously as a solution containing 5% of total protein. The amount of plasma protein fraction given will depend upon the clinical condition of the patient. For hypovolaemic shock an initial infusion of 250 to 500 mL has been suggested at a rate not normally exceeding 10 mL/minute. For doses used in children, see below. In hypoproteinaemia, 1 to 1.5 litres of a 5% solution will provide 50 to 75 g of protein. Patients with normal blood volume may require slow infusion to prevent excessive volume expansion.

As with other albumin solutions, plasma protein fraction should not be used for parenteral nutrition.

Administration in children. A 5% solution of plasma protein fraction may be given to infants and young children in the management of hypovolaemic shock. An initial dose of up to 33 mL/kg may be given by intravenous infusion, at a rate of up to 10 mL/minute. Doses should be adjusted according to the condition of the patient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Biseko; *Ger.*: Biseko; *Gr.*: Plasmanate†; *Hong Kong*: Plasmanate†; *Hung.*: Biseko; *Indon.*: Plasmanate; *Israel*: Plasmanate; *Ital.*: PPS; Uman-Serum; *Philipp.*: Plasmanate†; *S.Afr.*: Bioplasma FDP; *Singapore*: Plasmanate; *Thal.*: Biseko†; *Turk.*: Biseko; *USA*: Plasma-Plex; Plasmanate; Protenate.

Multi-ingredient Preparations. *Fin.*: Tisseel Duo Quick; *Ger.*: Tissucol Duo S; Tissucol-Kit; *Hung.*: Tissucol-Kit; *Ital.*: Tissucol; *Swed.*: Tisseel Duo Quick; *Switz.*: Tissucol Duo S†.

Pharmacopoeial Preparations

USP 36: Plasma Protein Fraction.

Platelets

Blodplader; Blodplater; Blodplättar; Bloedplaatjes; Blutplättchen; Piastrine; Plaquetas; Plaquettes; Płytek Krwi; Thrombocytes; Verihiutale; Тромбоциты.

Uses and Administration

Blood platelets assist in the haemostatic process (p. 1124.3) by aggregating to form a platelet thrombus, and by releasing factors involved in initiating coagulation.

Transfusions of platelet concentrates are given to patients with thrombocytopenic haemorrhage (see p. 1129.2). They are also given prophylactically to reduce the frequency of haemorrhage in thrombocytopenia associated with the chemotherapy of neoplastic disease (see p. 731.2).

References.
1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.
2. Schiffer CA, *et al.* Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1519–38. Also available at: http://jco.ascopubs.org/cgi/reprint/19/5/1519.pdf (accessed 13/08/10)
3. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; **122:** 10–23. Also available at: http://www.bcshguidelines.com/pdf/plateletstrans040703.pdf (accessed 27/10/05)
4. Heal JM, Blumberg N. Optimizing platelet transfusion therapy. *Blood Rev* 2004; **18:** 149–65.
5. Stroncek DF, Rebulla P. Platelet transfusions. *Lancet* 2007; **370:** 427–38.
6. Elebute M, *et al.* Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion*. 4th ed. Chichester: Wiley-Blackwell, 2009: 22–6.

Adverse Effects and Precautions

Transmission of infection has been associated with the transfusion of blood products including platelets (see Blood, p. 1135.3). Since platelets are stored at room temperature there is increased risk of bacterial infection after transfusion. Transfusion reactions including fever and urticaria are not uncommon. Recipients of multiple transfusions of platelet concentrates from random donors may develop antibodies to HLA which result in impaired responsiveness to subsequent transfusions. Use of leucocyte-depleted platelet concentrates reduces the incidence of transfusion reactions and of HLA sensitisation. Platelet concentrates prepared from Rh(D)-positive donors should generally not be given to Rh(D)-negative women of child-bearing potential. Ideally platelet concentrates should also be ABO-compatible with the recipient.

ABO compatibility. Platelets express the ABO blood group antigens and the plasma component of platelet concentrates may contain alloantibodies from the donor (see Blood Groups, p. 1136.3). Ideally, ABO-identical platelet concentrates should be used, but ABO-compatible concentrates are often used and incompatible concentrates may be used in an emergency. However, the use of ABO-mismatched platelets can reduce the efficacy of the platelet transfusion. Also, acute haemolytic reactions can occur after infusion of mismatched platelets if the infused

plasma contains high antibody titres or the volume of plasma infused is large. Some have suggested that screening donors for high antibody titres should be routine in order to avoid this, but there is no consensus as to the definition of critical titre. There have been mixed reports on whether the use of ABO-mismatched platelets has an effect on the recipient's long-term clinical course.

Reviews.
1. Lozano M, Cid J. The clinical implications of platelet transfusions associated with ABO or Rh(D) incompatibility. *Transfus Med Rev* 2003; 17: 57–68.

HLA antibodies. Platelets obtained from single donors have been used in patients receiving multiple transfusions of platelet concentrates to reduce the formation of antibodies to HLA. Some practitioners suggest[1] that patients who are likely to need long-term platelet support should be typed for HLA A and B antigens and screened for HLA antibodies. Leucocyte-depleted platelets and UVB-irradiated platelets have also been tried. A study[2] in 530 patients found that the incidence of platelet refractoriness was reduced from 13% of those patients receiving pooled platelet concentrates to 3% and 5% of those receiving leucocyte-depleted and UVB-irradiated platelets, respectively. A meta-analysis[3] of this and earlier small studies also concluded that leucocyte depletion reduced the risk of alloimmunisation and platelet refractoriness. Some guidelines[4] have nonetheless considered that there is no convincing evidence of clinical benefit from routine use.

1. Dan ME, Schiffer CA. Strategies for managing refractoriness to platelet transfusions. *Curr Hematol Rep* 2003; 2: 158–64.
2. The Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med* 1997; 337: 1861–9.
3. Vamvakas EC. Meta-analysis of randomized controlled trials of the efficacy of white cell reduction in preventing HLA-alloimmunization and refractoriness to random-donor platelet transfusions. *Transfus Med Rev* 1998; 12: 258–70.
4. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; 8: 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)

Plerixafor *(USAN, rINN)*

AMD-3100; JM-3100; Plerixafor; Plerixaforum; SDZ-SID-791; SID-791; Плериксафор.

1,1′-(1,4-Phenylenebismethylene)bis(1,4,8,11-tetraazacyclotetradecane).

$C_{28}H_{54}N_8$=502.8

CAS — 110078-46-1 (plerixafor); 155148-31-5 (plerixafor hydrochloride).

ATC — L03AX16.

ATC Vet — QL03AX16.

UNII — S91SPS499N.

Uses and Administration

Plerixafor is a CXCR4 chemokine receptor antagonist that blocks the binding of stromal cell-derived factor 1α. It inhibits the retention of haematopoietic stem cells in bone marrow, and increases their number in peripheral blood. In patients with non-Hodgkin's lymphoma or multiple myeloma, plerixafor is used, with granulocyte colony-stimulating factor (G-CSF), to mobilise stem cells for collection and subsequent autologous transplantation (see Haematopoietic Stem Cell Transplantation, p. 1937.1). G-CSF is given for 4 days before the first dose of plerixafor, and on each morning before apheresis. A dose of plerixafor 240 micrograms/kg is given by subcutaneous injection 6 to 11 hours before starting apheresis, usually for up to 4 consecutive days. The dose should not exceed 40 mg daily. For reduced doses to be used in renal impairment, see below.

References.
1. Holtan SG, *et al.* AMD3100 affects autograft lymphocyte collection and progression-free survival after autologous stem cell transplantation in non-Hodgkin lymphoma. *Clin Lymphoma Myeloma* 2007; 7: 315–18.
2. Gazitt Y, *et al.* Improved mobilization of peripheral blood CD34+ cells and dendritic cells by AMD3100 plus granulocyte-colony-stimulating factor in non-Hodgkin's lymphoma patients. *Stem Cells Dev* 2007; 16: 657–66.
3. Calandra G, *et al.* AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data. *Bone Marrow Transplant* 2008; 41: 331–8.
4. Cashen A, *et al.* A phase II study of plerixafor (AMD3100) plus G-CSF for autologous hematopoietic progenitor cell mobilization in patients with Hodgkin lymphoma. *Biol Blood Marrow Transplant* 2008; 14: 1253–61.
5. Wagstaff AJ. Plerixafor: in patients with non-Hodgkin's lymphoma or multiple myeloma. *Drugs* 2009; 69: 319–26.
6. DiPersio JF, *et al.* 3102 Investigators. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood* 2009; 113: 5720–6.
7. DiPersio JF, *et al.* 3101 Investigators. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol* 2009; 27: 4767–73.

Administration in renal impairment. In moderate and severe renal impairment (creatinine clearance 50 mL/min or less) the dose of plerixafor should be reduced to 160 micrograms/kg, given by subcutaneous injection 6 to 11 hours before apheresis, usually for up to 4 consecutive days. The daily dose should not exceed 27 mg. There is insufficient information to recommend doses for patients on haemodialysis.

Adverse Effects and Precautions

Adverse gastrointestinal effects are common with the use of plerixafor and include diarrhoea, nausea, vomiting, flatulence, abdominal distention or pain, dyspepsia, and dry mouth. Other common effects include fatigue, arthralgia, headache, dizziness, insomnia, hyperhidrosis, and erythema. Injection site reactions also occur frequently. Systemic reactions occurring within about 30 minutes of injection have been reported in a small number of patients, and include urticaria, periorbital swelling, dyspnoea, and hypoxia. Some cases of vasovagal reactions, orthostatic hypotension, and syncope, within 1 hour of injection, have also been reported. Based on studies showing splenic enlargement after plerixafor administration in *rats*, it is recommended that patients with left upper abdominal pain and/or scapular or shoulder pain should be investigated for splenic integrity.

As the use of plerixafor with granulocyte colony-stimulating factor increases circulating leucocytes, white blood cell counts should be monitored. Plerixafor should be used with caution when the neutrophil count is above 50 000 cells/microlitre. Thrombocytopenia has also occurred and platelet counts should be monitored. Plerixafor should not be used for stem cell mobilisation and collection in patients with leukaemia, as there is a risk of mobilising leukaemic cells which could contaminate the apheresis product.

Based on its mechanism of action, plerixafor has the potential to cause congenital malformations when given to pregnant women. Teratogenicity has been shown in *animal* studies.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies plerixafor as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

Peak plasma concentrations of plerixafor occur about 30 to 60 minutes after a subcutaneous dose. It is about 58% bound to plasma proteins and largely confined to the extravascular fluid space. Plerixafor is not metabolised. About 70% of a dose is eliminated in the urine within 24 hours after a dose, and the terminal plasma half-life is about 3 to 5 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Mozobil; *Austria*: Mozobil; *Belg.*: Mozobil; *Canad.*: Mozobil; *Cz.*: Mozobil; *Denm.*: Mozobil; *Fr.*: Mozobil; *Ger.*: Mozobil; *Gr.*: Mozobil; *Irl.*: Mozobil; *Israel*: Mozobil; *Neth.*: Mozobil; *Norw.*: Mozobil; *Pol.*: Mozobil; *Port.*: Mozobil; *Singapore*: Mozobil; *Spain*: Mozobil; *Swed.*: Mozobil; *UK*: Mozobil; *USA*: Mozobil.

Policresulen *(rINN)*

Acidum Metacresolsulfonicum c. Formaldehydo; *m*-Cresolsulphonic acid-formaldehyde condensation product; Dicresulene polymer; Dihydroxydimethyldiphenylmethanedisulphonic acid polymer; Formaldehydhaltig Metakresolsulfonsyra; Formaldehydipitoinen Metakresolisulfonihappo; Metacresolsulfonic Acid-Formaldehyde; Metacresolsulphonic Acid-Formaldehyde; Methylenebis(hydroxytoluenesulphonic acid) polymer; Policrésulène; Policresuleno; Policresulenum; Polikresuleeni; Polikresulen; Polímero de dicresuleno; Polycresolsulfonate; Поликрезулен.

α-(4-Hydroxy-2-methyl-5-sulfobenzyl)-ω-(4-hydroxy-5-sulfo-o-tolyl)poly[(4-hydroxy-2-methyl-5-sulfo-*m*-phenylene)methylene]; 2-Hydroxy-*p*-toluenesulfonic acid, polymer with formaldehyde.

$(C_8H_9O_4S)(C_8H_8O_4S)_n(C_7H_7O_4S)$

CAS — 9011-02-3; 101418-00-2.

ATC — D08AE02; G01AX03.

ATC Vet — QD08AE02; QG01AX03; QG51AD02.

Profile

Policresulen is used as a topical haemostatic and antiseptic. It is also used similarly in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Albocresil; *Braz.*: Albocresil; *China*: Albothyl (爱宝疗); *Cz.*: Vagothyl†; *Ger.*: Albothyl; *Hong Kong*: Albothyl; *Hung.*: Vagothyl; *Indon.*: Albothyl; *Ital.*: Emaftol; Negatol; *Malaysia*: Albothyl; *Mex.*: Albothyl; *Philipp.*: Albothyl; *Pol.*: Albothyl; Vagothyl; *Port.*: Nelex; *Rus.*: Vagotil (Ваготил); *Singapore*: Albothyl; *Switz.*: Negatol Dental.

Multi-ingredient Preparations. *Arg.*: Proctyl; *Braz.*: Proctox-H; Proctyl; *Cz.*: Faktu; *Ger.*: Faktu†; *Hong Kong*: Faktu; *Ind a*: Faktu; *Indon.*: Faktu; *Mex.*: Proctoacid; *Philipp.*: Faktu; *Port.*: Faktu; *Singapore*: Faktu; *Switz.*: Faktu.

Polygeline *(BAN, pINN)* ⊗

Poligelina; Polygéline; Polygelinum; Полигелин.

CAS — 9015-56-9.

ATC — B05AA10.

Description. Polygeline is a polymer prepared by cross-linking polypeptides derived from denatured gelatin with a di-isocyanate to form urea bridges.

Incompatibility. Intravenous preparations of polygeline contain calcium ions and are incompatible with citrated blood.

Uses and Administration

Polygeline is a plasma volume expander used as a 3.5% solution with electrolytes in the management of hypovolaemic shock (p. 1279.3). The rate of infusion depends on the condition of the patient and does not normally exceed 500 mL in 60 minutes although it may be greater in emergencies. Initial doses for hypovolaemic shock usually consist of 500 to 1000 mL; up to 1500 mL of blood loss can be replaced by polygeline alone. Patients losing greater volumes of blood will require blood transfusion as well as plasma expanders.

Polygeline is also used in extracorporeal perfusion fluids, as a perfusion fluid for isolated organs, as fluid replacement in plasma exchange, and as a carrier solution for insulin. For plasma exchange, up to 2 litres of polygeline may be given as sole replacement fluid.

Adverse Effects

As for Gelatin, p. 1154.2.

Hypersensitivity. Fatal reactions after polygeline infusion have been reported in 2 patients with bronchial asthma.[1,2] Both patients were undergoing epidural analgesia with bupivacaine and polygeline was given to correct hypotension that had not responded to infusion of crystalloids. One patient developed focal seizures.[2] Both patients developed refractory bronchospasm and cardiac arrhythmias and died despite intensive resuscitation attempts.

Licensed product information recommends that prophylaxis with histamine H_1- and H_2-antagonists should be given to patients with known allergic conditions such as asthma. Similar advice has been offered[3] for patients undergoing anaesthesia and receiving polygeline following findings of an increased incidence of severe histamine-related reactions in such patients. Nevertheless, severe respiratory distress developed in an asthmatic patient given polygeline under spinal anaesthesia despite premedication with bronchodilators and antihistamines.[4]

There is a possibility of cross reactivity between polygeline and succinylated gelatin (see Gelatin, p. 1154.2).

1. Freeman MK. Fatal reaction to haemaccel. *Anaesthesia* 1979; 34: 341–3.
2. Barratt S, Purcell GJ. Refractory bronchospasm following "Haemaccel" infusion and bupivacaine epidural anaesthesia. *Anaesth Intensive Care* 1988; 16: 208–11.
3. Lorenz W, *et al.* Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. *Lancet* 1994; 343: 933–40.
4. Kathirvel S, *et al.* Severe life threatening reaction to Haemaccel in a patient with bronchial asthma. *Eur J Anaesthesiol* 2001; 18: 122–3.

Precautions

Precautions that should be observed with plasma expanders are described under Dextran 70, p. 1139.2, and should be considered when polygeline is used for this purpose.

Polygeline preparations contain calcium ions and therefore should be used with caution in patients being treated with cardiac glycosides.

Pharmacokinetics

Like gelatin, polygeline is excreted mainly in the urine. The half-life is about 5 to 8 hours.

Renal impairment. In a study[1] in 52 patients with normal or impaired renal function given 500 mL of polygeline 3.5% about 50% of the dose was excreted in the urine within 48 hours in those with normal renal function. Excretion of polygeline in those with renal impairment, based on the patient's glomerular filtration rate (GFR), was found to be:

- GFR 31 to 90 mL/minute: unimpaired
- GFR 11 to 30 mL/minute: slightly reduced
- GFR 2 to 10 mL/minute: reduced to 27% in 48 hours
- GFR 0.5 to 2 mL/minute: reduced to 9.3% in 48 hours

The mean half-life of the elimination phase was 505 minutes in those with adequate renal function, increasing to 985 minutes in those with end-stage renal failure. Polygeline 500 mL of 3.5% solution could be given twice weekly for 1 to 2 months even in patients with total anuria.

1. Köhler H, *et al.* Elimination of hexamethylene diisocyanate cross-linked polypeptides in patients with normal or impaired renal function. *Eur J Clin Pharmacol* 1978; 14: 405–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Haemaccel; *Austral.*: Haemaccel; *Austria*: Haemaccel†; *Braz.*: Haemaccel; *Chile*: Elcel†; *Denm.*: Haemaccel; *Ger.*: Haemaccel†; *Gr.*: Haemaccel; *India*: Haemaccel; *Indon.*: Haemaccel; *Irl.*: Haemaccel; *Ital.*: Emagel; Gelplex; *Mex.*: Haemaccel; Phygelin†; *Neth.*: Haemaccel; *Norw.*: Haemaccel; *NZ*: Haemaccel; *Philipp.*: Plasmax; *Port.*: Haemaccel; *S.Afr.*: Haemaccel; *Singapore*: Haemaccel; *Thai.*: Haemaccel; Plasmax†; *UK*: Haemaccel†.

Protein C

Autoprothrombin IIA; Factor XIV; Proteína C; Протеин С

ATC — B01AD12.
ATC Vet — QB01AD12.
UNII — 3Z6S89TXPW.

Drotrecogin Alfa (Activated) *(BAN, USAN, rINN)*

Drotrecogina alfa (activada); Drotrécogine Alfa (activé); Drotrecoginum Alfa; Drotrecoginum Alfa (activatum); Drotrekogiinialfa; Drotrekogin Alfa; LY-203638; Дротрекогин Альфа (activated).

Recombinant human activated protein C (rh-APC).

CAS — 98530-76-8.
ATC — B01AD10.
ATC Vet — QB01AD10.
UNII — JGH8MYC891.

Incompatibility. In a simulated Y-site study,[1] only 6 of 34 drugs were found to be both physically and chemically compatible with drotrecogin alfa (activated); these were ceftriaxone, cisatracurium, fluconazole, glyceryl trinitrate, potassium chloride, and vasopressin. Drugs found to be incompatible were adrenaline hydrochloride, albumin, amiodarone hydrochloride, ampicillin with sulbactam, ceftazidime, ciclosporin, ciprofloxacin, clindamycin, dobutamine hydrochloride, dopamine hydrochloride, fosphenytoin, furosemide, gentamicin sulfate, heparin sodium, imipenem with cilastatin, insulin, levofloxacin, magnesium sulfate, metronidazole, midazolam hydrochloride, nitroprusside sodium, noradrenaline acid tartrate, piperacillin with tazobactam, potassium phosphate, ranitidine hydrochloride, ticarcillin with clavulanic acid, tobramycin sulfate, and vancomycin hydrochloride.

1. Mann HJ, *et al.* Physical and chemical compatibility of drotrecogin alfa (activated) with 34 drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; 61: 2664–71. Correction. *ibid.* 2005; 62: 1134.

Uses and Administration

Protein C is an endogenous inhibitor of blood coagulation (see Haemostasis and Fibrinolysis, p. 1124.3). A preparation of protein C purified from human plasma is used in the management of thromboembolic disorders, including coumarin-induced skin necrosis, in patients with congenital deficiency of protein C. The dose should be adjusted according to response in protein C activity; 100% activity should be targeted initially for acute therapy, then adjusted to be more than 25% for the duration of treatment. Licensed UK product information suggests an initial dose of 60 to 80 international units/kg. In the USA, an initial dose of 100 to 120 international units/kg is suggested for acute episodes and short-term prophylaxis of thromboembolism, followed by 3 doses of 60 to 80 units/kg every 6 hours, then maintenance doses of 45 to 60 units/kg every 6 or 12 hours. Doses of 45 to 60 units/kg every 12 hours are suggested for long-term prophylaxis. As a solution of 100 international units/mL it is given by intravenous injection at a maximum rate of 2 mL/minute.

For the use of protein C in children, see below.

Drotrecogin alfa (activated) is a recombinant activated protein C that has been used in the management of severe sepsis in high-risk patients with multiple organ failure. It is under investigation in the treatment of acute respiratory distress syndrome.

Administration in children. Dosage regimens of protein C used for children and neonates with protein C deficiency are the same as those used in adults (see above). However, for children weighing less than 10 kg the rate of injection should not exceed 0.2 mL/kg per minute.

Severe sepsis. Severe sepsis (sepsis associated with acute organ dysfunction; see Septicaemia, p. 203.2) involves a systemic inflammatory response, inappropriate coagulation, and impaired fibrinolysis. These contribute to the development of disseminated intravascular coagulation (DIC) and microvascular thrombosis (p. 1126.1). Endogenous protein C becomes depleted as it is activated in an attempt to restore homoeostasis. In the small number of cases that have been reported,[1-3] protein C replacement appeared to improve rate of survival and clinical outcome in the management of purpura fulminans and DIC in severe meningococcaemia. Protein C has also been used in a few patients with purpura fulminans associated with sepsis caused by other organisms such as *Streptococcus pneumoniae*.[4]

Drotrecogin alfa (activated) was studied in the management of severe sepsis and found to reduce morbidity and mortality, but with an increased risk of serious bleeding events[5-9] (see also Effects on the Blood, below). Pooled study data suggested that earlier treatment (within 24 hours of first organ dysfunction) was associated with more benefit than later treatment,[10] and subgroup analysis suggested that the benefits were greatest in those at greater risk of death.[11] A subsequent large, multicentre randomised study[12] (the ADDRESS trial) examined the effects of drotrecogin alfa (activated) in patients with severe sepsis but a low risk of death (APACHE II score less than 25, or single organ failure). The study was terminated early, as interim analysis indicated that there was no benefit from active therapy, and in the subgroup of patients with single organ failure who had undergone surgery within the last 30 days, those given the drug appeared to have a higher mortality rate than those assigned to placebo. Various regulatory bodies issued guidance restricting the use of drotrecogin alfa (activated) to high-risk patients under specialist care.[13-15] The PROWESS-SHOCK study subsequently found no survival benefit for patients with severe sepsis and septic shock, and drotrecogin alfa (activated) was voluntarily withdrawn in October 2011.[16]

Similar results to those in adults were reported in initial studies of drotrecogin alfa (activated) in children.[17,18] However, a large placebo-controlled study was stopped early when an interim analysis found that drotrecogin alfa (activated) was highly unlikely to show an improvement over placebo in the primary end-point of composite time to complete organ failure resolution over 14 days.[19] The analysis also found an increase in the rate of CNS bleeding in the drotrecogin alfa (activated) group.

1. Rintala E, *et al.* Protein C in the treatment of coagulopathy in meningococcal disease. *Lancet* 1996; 347: 1767.
2. Smith OP, *et al.* Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. *Lancet* 1997; 350: 1590–3.
3. Alberio L, *et al.* Protein C replacement in severe meningococcemia: rationale and clinical experience. *Clin Infect Dis* 2001; 32: 1338–46. Correction. *ibid.*; 1803.
4. Rintala E, *et al.* Protein C substitution in sepsis-associated purpura fulminans. *Crit Care Med* 2000; 28: 2373–8.
5. Bernard GR, *et al.* The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699–709.
6. Lyseng-Williamson KA, Perry CM. Drotrecogin alfa (activated). *Drugs* 2002; 62: 617–30.
7. Vincent J-L, *et al.* Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med* 2003; 31: 834–40.
8. Bernard GR, *et al.* Extended evaluation of recombinant human activated protein C United States Trial (ENHANCE US): a single-arm, phase 3B, multicenter study of drotrecogin alfa (activated) in severe sepsis. *Chest* 2004; 125: 2206–16.
9. Vincent J-L, *et al.* Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; 33: 2266–77.
10. Vincent J-L, *et al.* Use of an integrated clinical trial database to evaluate the effect of timing of drotrecogin alfa (activated) treatment in severe sepsis. *Crit Care* 2006; 10: R74.
11. Ely EW, *et al.* Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003; 31: 12–19.
12. Abraham E, *et al.* Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; 353: 1332–41.
13. NICE. Drotrecogin alfa (activated) for severe sepsis: Technology Appraisal 84 (September 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/TA084guidance.pdf (accessed 01/09/08)
14. EMEA Committee for Medicinal Products for Human Use. Press release (issued 21st April 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/12/WC500017772.pdf (accessed 16/08/10)
15. CHM/MHRA. Drotrecogin alfa (activated) (Xigris): risk-benefit in the management of sepsis. *Current Problems* 2006; 31: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 23/05/07)
16. Lilly. Lilly announces withdrawal of Xigris following recent clinical trial results (issued 25th October, 2011). Available at: https://investor.lilly.com/releasedetail2.cfm?ReleaseID=617602 (accessed 28/10/11)
17. Barton P, *et al.* Safety, pharmacokinetics, and pharmacodynamics of drotrecogin alfa (activated) in children with severe sepsis. *Pediatrics* 2004; 113: 7–17.
18. Goldstein B, *et al.* ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. *Pediatr Crit Care Med* 2006; 7: 200–211.
19. Nadel S, *et al.* REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007; 369: 836–43.

Adverse Effects and Precautions

As with other plasma-derived products, protein C preparations carry a risk of transmission of infection. Hypersensitivity reactions are possible. There have also been postmarketing reports of haemothorax, hypotension, hyperhidrosis, fever, and restlessness. Antibodies to protein C may develop in patients treated for congenital protein C deficiency.

Drotrecogin alfa (activated) may increase the risk of severe bleeding episodes. When used in patients with severe sepsis, it is therefore contra-indicated in those who are at low risk for death, such as those with single-organ failure, especially after surgery. It is also contra-indicated in patients with active internal bleeding and in those in which bleeding could be associated with a high risk of death or significant morbidity. Drotrecogin alfa (activated) should be used with caution when there is any other increased risk of bleeding. Drotrecogin alfa (activated) should be stopped 2 hours before any invasive surgery or procedure with an inherent risk of bleeding; it may be restarted 12 hours after major invasive procedures or surgery, or immediately after uncomplicated less invasive procedures, if adequate haemostasis has been achieved.

Effects on the blood. The safety data from early clinical studies and spontaneous reports during clinical use of drotrecogin alfa (activated) have been reviewed.[1] The overall rate of serious bleeding events was 5.3% during the 28-day study period. Serious bleeding events that were considered to be probably related to the use of drotrecogin alfa (activated) occurred in between 2.1% and 2.8% of patients, and often during the infusion period. Risks associated with serious bleeding events were invasive procedures and severe thrombocytopenia; meningitis may also be a risk factor for intracranial haemorrhage. It was recommended that drotrecogin alfa (activated) should not be used when the platelet count is less than 30 000/mm^3.

A subsequent large, multicentre, randomised study of drotrecogin alfa (activated) in patients with severe sepsis, but a low risk of death (the ADDRESS study), confirmed the increased incidence of bleeding in patients with single organ failure who had undergone recent surgery (within 30 days); these patients also had an increased death rate (see Severe Sepsis, above).

1. Bernard GR, *et al.* Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis. *Crit Care* 2003; 7: 155–63.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies protein C and drotrecogin alfa (activated) as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

When oral anticoagulants such as warfarin are started in patients receiving protein C replacement therapy, a transient hypercoagulable state may occur because of the rapid suppression of vitamin K-dependent protein C activity. An initial low dose of the oral anticoagulant should be increased gradually, and protein C replacement continued, until anticoagulation is stabilised. The risk of bleeding may be increased if tissue plasminogen activator and protein C are used together.

The risk of bleeding with drotrecogin alfa (activated) may be increased if it is used with other drugs that affect haemostasis, such as thrombolytics, oral anticoagulants, antiplatelet drugs, glycoprotein IIb/IIIa-receptor antagonists, and prostacyclins. Low doses of heparin for venous thromboembolism prophylaxis may be used with drotrecogin alfa (activated) without increased risk of serious bleeding. However, in a study of patients with severe sepsis who were already receiving prophylactic heparin, the risks of death and serious adverse events were increased if heparin was stopped when drotrecogin alfa (activated) was started; the reason for this was unclear.

Pharmacokinetics

In patients with protein C deficiency, the terminal half-life of administered protein C may range from about 5 to 15

hours. The half-life may be considerably reduced in patients with acute thrombosis. Systemic exposure may also be reduced in very young children.

During continuous infusion for the management of severe sepsis, steady-state plasma concentrations of drotrecogin alfa (activated) occur in about 2 hours. It is inactivated by plasma protease inhibitors and rapidly cleared from the circulation, falling to below measurable limits within about 2 hours of stopping the infusion.

References.
1. Macias WL, *et al.* Pharmacokinetic-pharmacodynamic analysis of drotrecogin alfa (activated) in patients with severe sepsis. *Clin Pharmacol Ther* 2002; 72: 391–402.
2. Levy H, *et al.* Obesity does not alter the pharmacokinetics of drotrecogin alfa (activated) in severe sepsis. *Ann Pharmacother* 2005; 39: 262–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Xigris†; *Austral.*: Xigris†; *Austria*: Ceprotin; Xigris†; *Belg.*: Ceprotin; Xigris†; *Braz.*: Xigris†; *Canad.*: Xigris†; *Chile*: Xigris†; *Cz.*: Ceprotin; Xigris†; *Denm.*: Xigris†; *Fin.*: Ceprotin; Xigris†; *Fr.*: Protexel; Xigris†; *Ger.*: Ceprotin; Xigris†; *Gr.*: Ceprotin; Xigris; *Hong Kong*: Xigris†; *Hung.*: Xigris†; *India*: Xigris†; *Irl.*: Ceprotin; Xigris†; *Israel*: Xigris†; *Ital.*: Ceprotin; Xigris†; *Jpn*: Anact C; *Malaysia*: Xigris†; *Mex.*: Xigris†; *Neth.*: Ceprotin; Xigris†; *Norw.*: Ceprotin†; Xigris†; *NZ*: Xigris†; *Pol.*: Ceprotin; Xigris†; *Port.*: Ceprotin; Xigris†; *Rus.*: Ceprotin (Сепротин); Xigris (Зигрис)†; *S.Afr.*: Xigris†; *Singapore*: Xigris†; *Spain*: Ceprotin; Xigris†; *Swed.*: Ceprotin; Xigris†; *Switz.*: Ceprotin; Xigris†; *Turk.*: Xigris†; *UK*: Ceprotin; Xigris†; *USA*: Ceprotin; Xigris†; *Venez.*: Xigris†.

Red Blood Cells ⊗

Eritrociták; Eritrociti; Eritrócitos; Eritrocitos; Erythrocytes; Érythrocytes; Erythrocyti; Erythrozyten; Erytrocyten; Erytrocyter; Erytrocytów; Erytrocytter; Globules Rouges; Globuli Rossi; Glóbulos rojos; Glóbulos Vermelhos; Røde Blodceller; Röda Blodkroppar; Rode Bloedcel; Roten Blutkörperchen; Vörösvértestek; Эритроциты.

ATC — B05AX01.
UNII — 2K524Y8G0J.

Uses and Administration

Transfusions of red blood cells are given for the treatment of severe anaemia without hypovolaemia (p. 1121.2).

Red blood cells are also used for exchange transfusion in babies with haemolytic disease of the newborn (p. 2377.2). Red cells may be used with volume expanders for acute blood loss of less than half of the blood volume; if more than half of the blood volume has been lost, whole blood should be used.

Other red blood cell products are available. Concentrated red cells in an optimal additive solution containing sodium chloride, adenine, glucose, and mannitol has reduced viscosity and an extended shelf-life. Leucocyte-depleted red cells may be used in patients who have developed antibodies to previous transfusions or in whom development of antibodies is undesirable. Frozen, thawed, and washed red cell concentrates in which plasma proteins are removed in addition to leucocytes and platelets may be used in patients with rare antibodies.

Reviews and guidelines.

1. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; 8: 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)
2. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; 113: 24–31. Also available at: http://www.bcshguidelines.com/pdf/bjh2701.pdf (accessed 27/10/05)
3. Hill SR, *et al.* Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 16/06/05).
4. Klein HG, *et al.* Red blood cell transfusion in clinical practice. *Lancet* 2007; 370: 415–26.
5. Morley SL. Red blood cell transfusions in acute paediatrics. *Arch Dis Child Educ Pract Ed* 2009; 94: 65–73.
6. Murphy M, Wallis J. Red cell transfusion. In: Contreras M, ed. *ABC of transfusion*. 4th ed. Chichester: Wiley-Blackwell, 2009: 15–21.

Adverse Effects and Precautions

As for Blood, p. 1135.3.

Antibody formation. Patients with sickle-cell anaemia frequently require repeated transfusions of red blood cells. Alloimmunisation is a common problem in these patients, and has the potential to cause haemolytic transfusion reactions.[1] Alloantibodies were detected in 32 of 107 black patients with sickle-cell anaemia who had received red cell transfusions compared with 1 of 19 non-black patients who had received transfusions for other chronic anaemias.[2] The incidence of antibody formation was related to the number of transfusions received. An analysis of the red cell phenotypes suggested that the high rate of alloimmunisation among patients with sickle-cell anaemia could be due to racial differences between donors and recipients. Alloimmunisation can also occur in thalassaemia patients who are given transfusions,[3] and the incidence in these patients may also be affected by racial differences between donors and recipients.[4] Erythrocyte autoantibody formation has also been reported.[1,3]

1. Aygun B, *et al.* Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion* 2002; 42: 37–43.
2. Vichinsky EP, *et al.* Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *N Engl J Med* 1990; 322: 1617–21.
3. Singer ST, *et al.* Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. *Blood* 2000; 96: 3369–73.
4. Ho H-K, *et al.* Alloimmunization in Hong Kong southern Chinese transfusion-dependent thalassemia patients. *Blood* 2001; 97: 3999–4000.

Romiplostim *(BAN, USAN, rINN)*

AMG-531; Romiplostimum; Ромиплостим.

L-Methionyl[human immunoglobulin heavy constant gamma 1-(227 C-terminal residues)-peptide (Fc fragment)] fusion protein with 41 amino acids peptide, (7-7':10,10')-bisdisulfide dimer.

CAS — 267639-76-9.
ATC — B02BX04.
ATC Vet — QB02BX04.
UNII — GN5XU2DXKV.

Uses and Administration

Romiplostim is an Fc-peptide fusion protein that acts as an agonist at the thrombopoietin receptor to stimulate platelet production; it has no amino acid sequence homology with endogenous thrombopoietin. Romiplostim is used to treat thrombocytopenia in patients with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura; p. 1606.1). It should only be used when the response to treatment with corticosteroids, immunoglobulins, or splenectomy has been insufficient, and the patient is at increased risk of bleeding. Romiplostim should not be used in an attempt to normalise platelet counts. The safety and efficacy of romiplostim have not been established for patients younger than 18 years old, but see below for some references to use in children.

The initial dose of romiplostim is 1 microgram/kg given by subcutaneous injection. This is repeated once weekly, and adjusted by increments of 1 microgram/kg to raise the platelet count to at least 50×10^9 cells/litre as necessary to reduce the risk of bleeding. The weekly dose should not exceed 10 micrograms/kg. All doses should be calculated using the patient's actual body-weight at the start of treatment.

- UK licensed product information recommends that the dose should be reduced by 1 microgram/kg if the count is higher than 150×10^9 cells/litre for 2 consecutive weeks (US information suggests a threshold of 200×10^9 cells/litre).
- Romiplostim should be withheld and platelet counts measured weekly if the count is higher than 250×10^9 cells/litre (US threshold 400×10^9 cells/litre); treatment may be restarted at a dose reduced by 1 microgram/kg when the count has fallen below 150×10^9 cells/litre (200×10^9 cells/litre in the USA).
- Romiplostim should be stopped if the platelet count is not raised sufficiently to avoid clinically important bleeding after 4 weeks of treatment at the maximum weekly dose of 10 micrograms/kg.

Complete blood counts, including platelet counts and peripheral blood smears, should be assessed weekly during dosage adjustment, and monthly during stable romiplostim therapy. Complete blood counts, including platelet counts, should be monitored weekly for at least 2 weeks after stopping romiplostim (see also below).

References.
1. Bussel JB, *et al.* AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006; 355: 1672–81. Correction. *ibid.*: 2054.
2. Kuter DJ, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; 371: 395–403.
3. Frampton JE, Lyseng-Williamson KA. Romiplostim. *Drugs* 2009; 69: 307–17.
4. Bussel JB, *et al.* Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood* 2009; 113: 2161–71. Correction. *ibid.*: 4822.
5. Ipema HJ, *et al.* Romiplostim management of immune thrombocytopenic purpura. *Ann Pharmacother* 2009; 43: 914–19.
6. Kuter DJ, *et al.* Romiplostim or standard of care in patients with immune thrombocytopenia. *N Engl J Med* 2010; 363: 1889–99.
7. NICE. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (issued April 2011). Available at: http://www.nice.org.uk/nicemedia/live/13467/54219/54219.pdf (accessed 19/10/11)
8. Zeng Y, *et al.* TPO receptor agonist for chronic idiopathic thrombocytopenic purpura. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2011 (accessed 19/10/11).

Administration in children. Romiplostim has been studied in the treatment of thrombocytopenia in children with chronic immune thrombocytopenia, using similar dosage regimens to those used in adults (see Uses and Administration, above).[1,2]

1. Elalfy MS, *et al.* Romiplostim in children with chronic refractory ITP: randomized placebo controlled study. *Ann Hematol* 2011; 90: 1341–4.
2. Bussel JB, *et al.* A randomized, double-blind study of romiplostim to determine its safety and efficacy in children with immune thrombocytopenia. *Blood* 2011; 118: 28–36.

Adverse Effects and Precautions

Adverse effects of romiplostim include headache, arthralgia, myalgia, pain in the extremities, abdomen, back, or shoulder, dizziness, insomnia, gastrointestinal disturbance, and paraesthesia. Skin reactions have included pruritus, ecchymosis, and rash, as well as injection-site reactions and haemorrhage.

Excessive increases in platelet counts may lead to thrombosis or thromboembolism. Cases of thromboembolism, including portal vein thrombosis, have been reported in patients with chronic liver disease, and romiplostim should only be used in patients with moderate to severe hepatic impairment (Child-Pugh score of 7 or more) when the expected benefit outweighs this risk.

Romiplostim increases the risk for the development or progression of reticulin fibre deposition in the bone marrow, and a risk of bone marrow fibrosis with cytopenias has not been excluded. The level of cellular morphological abnormalities should be established before starting romiplostim and monitored monthly during stable therapy. Romiplostim should be stopped if new or worsening abnormalities or cytopenias develop.

Romiplostim should not be used to treat thrombocytopenia due to myelodysplastic syndrome because of the risks of transient increases in peripheral blast cell counts and progression to acute myeloid leukaemia, which have been reported in studies of romiplostim.

When romiplostim is stopped, thrombocytopenia may become worse than before treatment was started. As this may increase the risk of bleeding, complete blood counts (including platelet counts) should be monitored weekly for at least 2 weeks after romiplostim is stopped.

Neutralising antibodies may reduce the efficacy of romiplostim.

Effects on the peripheral circulation. Erythromelalgia of the hands and feet occurred within 48 hours after an initial dose of romiplostim in a 59-year-old man.[1] The condition recurred after each weekly dose, and subsided within a few days.

1. Kluger N, *et al.* Romiplostim-induced erythromelalgia in a patient with idiopathic thrombocytopenic purpura. *Br J Dermatol* 2009; 161: 482–4.

Pharmacokinetics

During weekly subcutaneous treatment, peak serum-romiplostim concentrations occur about 7 to 50 hours after a dose (median 14 hours), and the half-life has ranged from 1 to 34 days (median 3.5 days). Serum concentration varies and is, in part, dependent on binding to the thrombopoietin receptor on platelets, such that higher platelet counts are associated with lower serum concentrations of romiplostim and vice versa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Nplate; *Austria*: Nplate; *Belg.*: Nplate; *Canad.*: Nplate; *Cz.*: Nplate; *Denm.*: Nplate; *Fr.*: Nplate; *Ger.*: Nplate; *Gr.*: Nplate; *Hung.*: Nplate; *Irl.*: Nplate; *Israel*: Nplate; *Jpn*: Romiplate; *Neth.*: Nplate; *Norw.*: Nplate; *Pol.*: Nplate; *Port.*: Nplate; *Spain*: Nplate; *Swed.*: Nplate; *UK*: Nplate; *USA*: Nplate.

Sargramostim *(BAN, USAN, rINN)*

BI-61.012; rhu GM-CSF; Sargramostimum; Сарграмостим.

A recombinant human granulocyte-macrophage colony-stimulating factor; 23-L-Leucinecolony-stimulating factor 2 (human clone pHG_{23} protein moiety).

CAS — 123774-72-1.
ATC — L03AA09.
ATC Vet — QL03AA09.
UNII — 5TAA004E22.

Pharmacopoeias. In *US*.

USP 36: (Sargramostim). A single chain, glycosylated polypeptide of 127 amino acid residues expressed from *Saccharomyces cerevisiae*. The glycoprotein mainly consists of 3 molecular species having relative molecular weights of about 19 500, 16 800, and 15 500 due to different levels of glycosylation. Sargramostim has the property of generating granulocyte, macrophage, and mixed granulocyte macrophage colonies from haematopoietic progenitor cells found

in bone marrow. Store in sealed containers at a temperature of -20 degrees or below.

Stability. Solutions of sargramostim may be adsorbed onto glass or plastic materials and so albumin must be added to give a final concentration of 1 mg/mL to solutions that are diluted to concentrations of sargramostim below 10 micrograms/mL.

Uses and Administration

Sargramostim is a granulocyte-macrophage colony-stimulating factor with actions and uses similar to those of molgramostim (p. 1156.2). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p. 731.1). It is also used after bone marrow transplantation when engraftment is delayed or has failed. Sargramostim may be used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous peripheral blood stem cell transplantation, as well as after transplantation to improve engraftment.

As an **adjunct to antineoplastic therapy**, sargramostim is given by intravenous infusion over 4 hours in a dose of 250 micrograms/m² daily for up to 42 days as required.

After **bone marrow transplantation**, sargramostim may be given in a dose of 250 micrograms/m² daily by intravenous infusion over 2 hours. When engraftment is delayed or has failed, a course of sargramostim 250 micrograms/m² daily for 14 days may be used. The dose can be repeated after a 7-day interval if engraftment has not occurred. A third course of 500 micrograms/m² daily for 14 days may be tried after another 7-day interval if needed, but further dose escalation is unlikely to be of benefit.

For **mobilisation** of peripheral blood progenitor cells a dose of 250 micrograms/m² daily is given by continuous intravenous infusion over 24 hours or by subcutaneous injection, with leucapheresis usually starting on day 5. The same dosing regimen may be used after peripheral blood stem cell transplantation, until neutrophil recovery.

HIV infection and AIDS. Sargramostim has been evaluated in the management of HIV infection (p. 957.2). There is some evidence to suggest that it might help to decrease and suppress viral load, and increase CD4+ cell counts, by enhancing the activity of antiretroviral drugs and increasing the resistance of monocytes to HIV infection.[1-3] However, in a study[4] of patients who were medically stable but had incompletely controlled HIV replication, sargramostim did not have a significant antiviral effect and there was only a trend towards increased CD4+ counts. A small study[5] found that molgramostim blunted viral rebound after interruption of HAART.

1. Skowron G, *et al.* The safety and efficacy of granulocyte-macrophage colony-stimulating factor (sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. *J Infect Dis* 1999; 180: 1064–71.
2. Brites C, *et al.* A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and nucleoside analogue therapy in AIDS. *J Infect Dis* 2000; 182: 1531–5.
3. Angel JB, *et al.* Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. *AIDS* 2000; 14: 387–95.
4. Jacobson JM, *et al.* Granulocyte-macrophage colony-stimulating factor induces modest increases in plasma human immunodeficiency virus (HIV) type 1 RNA levels and CD4+ lymphocyte counts in patients with uncontrolled HIV infection. *J Infect Dis* 2003; 188: 1804–14.
5. Fagard C, *et al.* A controlled trial of granulocyte macrophage-colony stimulating factor during interruption of HAART. *AIDS* 2003; 17: 1487–92.

Inflammatory bowel disease. A small dose-escalating study[1] reported a beneficial effect from the use of sargramostim in Crohn's disease (see Inflammatory Bowel Disease, p. 1811.3). A subsequent larger placebo-controlled study[2] in moderate to severe active disease found that the rate of response to sargramostim was not significantly different from that of placebo. Although disease severity and quality of life improved in the sargramostim group, later unpublished study results were said to be disappointing, and in June 2007 the manufacturer declared that it would not be investigating sargramostim any further in Crohn's disease.

1. Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; 360: 1478–80.
2. Korzenik JR, *et al.* Sargramostim for active Crohn's disease. *N Engl J Med* 2005; 352: 2193–2201.

Malignant neoplasms. It has been suggested that granulocyte-macrophage colony-stimulating factor may be able to increase antitumour immune activity. Sargramostim, given by nebuliser to stimulate a local response, has been investigated in patients with lung metastases.[1,2]

1. Anderson PM, *et al.* Aerosol granulocyte macrophage-colony stimulating factor: a low toxicity, lung-specific biological therapy in patients with lung metastases. *Clin Cancer Res* 1999; 5: 2316–23.
2. Rao RD, *et al.* Aerosolized granulocyte macrophage colony-stimulating factor (GM-CSF) therapy in metastatic cancer. *Am J Clin Oncol* 2003; 26: 493–8.

Respiratory disorders. See under Molgramostim (p. 1156.3) for mention of the use of sargramostim in pulmonary alveolar proteinosis.

Wounds and ulcers. See under Molgramostim (p. 1156.3) for mention of the use of sargramostim in the promotion of wound healing.

Adverse Effects and Precautions

As for Molgramostim, p. 1156.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Leukine.

Pharmacopoeial Preparations
USP 36: Sargramostim for Injection.

Thrombin *(rINN)*

Factor IIa; Thrombine; Thrombinum; Trombin; Trombina; Тромбин.
CAS — 9002-04-4.
ATC — B02BC06; B02BD30.
ATC Vet — QB02BC06; QB02BD30.
UNII — 2SADE2236L.

Thrombin Alfa *(USAN, rINN)*

Human thrombin (recombinant, glycosylated); Thrombine Alfa; Thrombinum Alfa; Trombina alfa; Тромбин Альфа.
Human thrombin (recombinant, glycofrom α).
CAS — 869858-13-9.
UNII — SCK81AMR7R.

Uses and Administration

Thrombin is a protein substance produced *in vivo* from prothrombin that converts soluble fibrinogen into insoluble fibrin thus producing coagulation.

Thrombin of either human or bovine origin is applied topically to control bleeding from capillaries and small venules. It is applied directly to the bleeding surface either as a solution or dry powder. It may also be used with absorbable gelatin sponge during surgical procedures. Thrombin alfa, a recombinant human thrombin, is used similarly.

Thrombin is a component of fibrin glue (p. 1151.2).

General references. Reviews.
1. Lundblad RL, *et al.* A review of the therapeutic uses of thrombin. *Thromb Haemost* 2004; 91: 851–60.

Pseudoaneurysm. An acute pseudoaneurysm is an arterial rupture, contained by fibromuscular tissue, that communicates with the artery via a narrow neck. Insertion-site femoral pseudoaneurysm can occur as a result of procedures such as cardiac catheterisation and peripheral angiography. It is usually treated with ultrasound-guided compression, but this time-consuming technique causes discomfort for both the patient and the staff carrying out the procedure, and may be of limited success for large pseudoaneurysms and patients receiving anticoagulation. Surgical repair may be required in some patients. As an alternative to pressure or surgery, thrombin has been given by ultrasound-guided percutaneous injection. In reported series,[1-4] complete thrombosis of the pseudoaneurysm sac occurred in more than 90% of patients with one injection of bovine thrombin. Bovine thrombin has also been used when compression has failed,[4,5] and a comparative study[6] in 30 patients found thrombin to be more successful than compression. Human thrombin has also been used successfully.[7] A retrospective review[8] concluded that bovine and human thrombin were equally effective. The successful use of autologous thrombin in a few patients has also been described.[9]

1. La Perna L, *et al.* Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. *Circulation* 2000; 102: 2391–5.
2. Mohler ER, *et al.* Therapeutic thrombin injection of pseudoaneurysms: a multicenter experience. *Vasc Med* 2001; 6: 241–4.
3. Olsen DM, *et al.* A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 2002; 36: 779–82.
4. Stone P, *et al.* Iatrogenic pseudoaneurysms: comparison of treatment modalities, including duplex-guided thrombin injection. *W V Med J* 2003; 99: 230–2.
5. Lönn L, *et al.* Treatment of femoral pseudoaneurysms: percutaneous US-guided thrombin injection versus US-guided compression. *Acta Radiol* 2002; 43: 396–400.
6. Lönn L, *et al.* Prospective randomized study comparing ultrasound-guided thrombin injection to compression in the treatment of femoral pseudoaneurysms. *J Endovasc Ther* 2004; 11: 570–6.
7. Maleux G, *et al.* Percutaneous injection of human thrombin to treat iatrogenic femoral pseudoaneurysms: short- and midterm ultrasound follow-up. *Eur Radiol* 2003; 13: 209–12.
8. Vázquez V, *et al.* Human thrombin for treatment of pseudoaneurysms: comparison of bovine and human thrombin sonogram-guided injection. *Am J Roentg* 2005; 184: 1665–71.
9. Quarmby JW, *et al.* Autologous thrombin for treatment of pseudoaneurysms. *Lancet* 2002; 359: 946–7.

Adverse Effects and Precautions

Hypersensitivity reactions, including anaphylaxis, have occurred rarely. Thrombin solutions must not be injected into blood vessels.

Antibody formation. Exposure to thrombin preparations of bovine origin has led to the development of antibodies to bovine thrombin and factor V with cross-reactivity, in some cases, to human factors. The presence of inhibitors to human factors may produce bleeding abnormalities and interfere with clotting measurements. Platelet infusions, fresh frozen plasma, and activated prothrombin complex concentrates have been used in the management of acute haemorrhagic complications, though often with limited success. Treatments that have been tried, in order to reduce the antibody titre, have included corticosteroids, ciclosporin, antineoplastics, intravenous immunoglobulin, and plasmapheresis.[1,2] Despite the availability of preparations containing virus-inactivated human fibrinogen the use of bovine thrombin is reported to be widespread and cases of acquired factor V inhibitor continue to occur.[3]

1. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. *J Lab Clin Med* 1999; 133: 326–34.
2. Streiff MB, Ness PM. Acquired FV inhibitors: a needless iatrogenic complication of bovine thrombin exposure. *Transfusion* 2002; 42: 18–26.
3. Kirkeby KM, Aronowitz P. Acquired factor V inhibitor: a common and avoidable complication of topical bovine thrombin application. *Am J Med* 2005; 118: 805.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Recothrom; *China*: Kang Li Ning (康立宁); ShuPing LaiShi (舒平莱士); Siduopu (斯多普); *NZ*: Thrombostat†; *Pol.*: BioTrombina; Gastrotrombina; *S.Afr.*: Tisseel†; *Singapore*: Thrombostat; *USA*: Evithrom; Recothrom; Thrombi-Gel; Thrombi-Pad; Thrombinar; Thrombostat.

Multi-ingredient Preparations. *Arg.*: Beriplast P; Tissucol; *Austral.*: Tisseel Duo†; *Austria*: Beriplast; Evicel; TachoSil; Tisseel; Tissucol Duo Quick†; Tissucol†; *Belg.*: Artiss; Quixil†; TachoSil; Tissucol Duo; Tissucol Kit; *Braz.*: Beriplast P; TachoSil; *Canad.*: Artiss; Tisseel; *Chile*: Beriplast P†; *China*: FibinGluRAAS (护固莱士); *Cz.*: Artiss; Evicel; TachoSil; Tisseel; Tissucol; *Denm.*: Artiss; Evicel; Quixil; TachoSil; Tisseel Duo Quick; *Fin.*: Artiss; Quixil; TachoSil; Tisseel Duo Quick; Tisseel; *Fr.*: Artiss; Beriplast; Evicel; Quixil†; TachoSil; Tissucol; *Ger.*: Artiss; Beriplast; Evicel; Quixil†; TachoSil; Tissucol Duo S; Tissucol-Kit; *Gr.*: Beriplast; Evicel; TachoSil; Tisseel; *Hong Kong*: Beriplast P; TachoComb; Tisseel; *Hung.*: Beriplast P; TachoSil; Tissucol-Kit; *Indon.*: Beriplast; *Irl.*: Artiss; Evicel; TachoSil; Tisseel; *Israel*: Beriplast†; Evicel; Quixil†; TachoSil; Thrombixil; Tisseel†; *Ital.*: Beriplast; Quixil; TachoSil; Tissucol; *Jpn*: Bolheal; TachoSil; *Mex.*: Beriplast P; *Neth.*: Artiss; Beriplast P; Quixil†; TachoSil; Tisseel; Tissucol Duo; Tissucol; *Norw.*: Artiss; Evicel; TachoSil; Tisseel; *NZ*: Tisseel Duo; *Pol.*: Beriplast; Evicel; TachoSil; *Port.*: Evicel; Quixil†; TachoSil; Tissucol Duo†; *Rus.*: TachoComb (ТахоКомб); Tissucol Kit (Тиссукол Кит); *Singapore*: TachoComb; *Spain*: Artiss; Beriplast P Combi; Evicel; TachoSil; Tissucol Duo; *Swed.*: Artiss; Evicel; Quixil†; TachoSil; Tisseel Duo Quick; *Switz.*: Artiss; Beriplast P; Evicel; Quixil; TachoSil; Tisseel; Tissucol Duo S†; Tissucol†; *Thai.*: Fibingluraas; Tisseel; *Turk.*: Beriplast P; Tisseel VH; *UK*: TachoSil; Tisseel; *Ukr.*: TachoComb (Тахокомб); *USA*: Artiss; Evarrest; Evicel; TachoSil; Tisseel.

Pharmacopoeial Preparations
Ph. Eur.: Fibrin Sealant Kit.

Thrombomodulin Alfa *(rINN)*

ART-123; Thrombomoduline Alfa; Thrombomodulinum Alfa; Trombomodulina alfa; Тромбомодулин Альфа.
1–498-Thrombomodulin (human clone TMP26/TMJ1 protein moiety reduced).
CAS — 120313-91-9.

NOTE. The name Recomodulin has been used as a trade mark for thrombomodulin alfa.

Profile

Endogenous thrombomodulin is a transmembrane protein found on the surface of endothelial cells, which acts as a thrombin receptor. Thrombomodulin-bound thrombin activates protein C, which then inactivates clotting factors and so limits coagulation.

Thrombomodulin alfa, a recombinant form of thrombomodulin, is under investigation in the prophylaxis of venous thromboembolism and is used in the treatment of disseminated intravascular coagulation.

References.
1. Kearon C, *et al.* Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2005; 3: 962–8.
2. Saito H, *et al.* Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 2007; 5: 31–41.
3. Ogawa E, *et al.* Successful treatment of disseminated intravascular coagulation in a child with acute myelogenous leukaemia using recombinant thrombomodulin. *Br J Haematol* 2010; 149: 911–12.

Thromboplastin

Citozima; Cytozyme; Thrombokinase; Trombocinasa; Tromboplastina; Tromboplastyna; Tromboquinasa; Тромбопластин.

UNII — 1U5PI2DLU1.

Profile

Tissue thromboplastin (tissue factor; factor III) is a membrane glycoprotein that is released from damaged tissue and initiates coagulation. The term thromboplastin may also be applied to other related substances with similar activity. Commercial preparations may contain tissue extracts comprising a variety of such substances.

Preparations of thromboplastin have been used as haemostatics.

A preparation of thromboplastin derived from rabbit brain is used in the determination of the prothrombin time for the control of anticoagulant therapy (for further details see Uses and Administration of Warfarin Sodium, p. 1527.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Clauden.

Multi-ingredient Preparations. *Braz.*: Claudemor.

Thrombopoietin

Trombopoietina; Trombopoyetina; Тромбопоэтин.

Profile

Thrombopoietin is a naturally occurring colony-stimulating factor that regulates thrombopoiesis (see Haematopoiesis, p. 1121.1). Recombinant thrombopoietin, and a form of recombinant thrombopoietin conjugated with polyethylene glycol (pegacaristim, PEG-megakaryocyte growth and development factor, PEG-rHuMGDF), are under investigation. They have been studied in the management of thrombocytopenia (p. 1129.2) in patients receiving myelosuppressive or myeloablative chemotherapy, and in patients with myelodysplastic syndrome or HIV-associated thrombocytopenia. There is also some interest in the use of recombinant forms of thrombopoietin in stem cell mobilisation regimens and to increase platelet counts in healthy apheresis donors. However, some results have been disappointing and there are reports of neutralising antibody development.

General references. Studies and reviews.

1. Vadhan-Raj S, *et al.* Safety and efficacy of transfusions of autologous cryopreserved platelets derived from recombinant human thrombopoietin to support chemotherapy-associated severe thrombocytopenia: a randomised cross-over study. *Lancet* 2002; 359: 2145–52.
2. Nomura S, *et al.* Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. *Blood* 2002; 100: 728–30.
3. Schuster MW, *et al.* The effects of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet recovery in breast cancer patients undergoing autologous bone marrow transplantation. *Exp Hematol* 2002; 30: 1044–50.
4. Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. *Blood* 2002; 100: 3457–69.
5. Linker C, *et al.* Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplantation. *Biol Blood Marrow Transplant* 2003; 9: 405–13.
6. Vadhan-Raj S, *et al.* Importance of predosing of recombinant human thrombopoietin to reduce chemotherapy-induced early thrombocytopenia. *J Clin Oncol* 2003; 21: 3158–67.
7. Geissler K, *et al.* Prior and concurrent administration of recombinant human megakaryocyte growth and development factor in patients receiving consolidation chemotherapy for de novo acute myeloid leukemia—a randomized, placebo-controlled, double-blind safety and efficacy study. *Ann Hematol* 2003; 82: 677–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Te Bi Ao (特比澳); *Philipp.*: Tpiao.

Tranexamic Acid *(BAN, USAN, rINN)*

Acide Tranexamique; Ácido tranexámico; Acidum Tranexamicum; AMCA; *trans*-AMCHA; CL-65336; Kyselina tranexamová; Traneksaamihappo; Traneksamik Asit; Traneksamo rūgštis; Tranexámico, ácido; Tranexamsäure; Tranexámsav; Tranexamsyra; Транексамовая Кислота.

trans-4-(Aminomethyl)cyclohexanecarboxylic acid.

$C_8H_{15}NO_2$=157.2

CAS — 1197-18-8.

ATC — B02AA02.

ATC Vet — QB02AA02.

UNII — 6T84R30KC1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tranexamic Acid). A white or almost white, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 7.0 to 8.0.

USP 36: (Tranexamic Acid). White, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. Store in airtight containers at a temperature not exceeding 30 degrees.

Incompatibility. Solutions of tranexamic acid are incompatible with benzylpenicillin, and should not be added to blood for transfusion.

Uses and Administration

Tranexamic acid is an antifibrinolytic drug that inhibits breakdown of fibrin clots. It acts mainly by blocking the binding of plasminogen and plasmin to fibrin; direct inhibition of plasmin occurs only to a limited degree. Tranexamic acid is used in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It is also used in the prophylaxis of hereditary angioedema.

Tranexamic acid is given orally and by slow intravenous injection or continuous infusion. Parenteral dosage is usually changed to oral after a few days. Alternatively, an initial intravenous injection may be followed by continuous infusion.

For short-term use in localised **haemorrhage** (below), usual oral doses are 1 to 1.5 g (or 15 to 25 mg/kg) 2 or 3 times daily. For slow intravenous injection, doses of 0.5 to 1 g are given 3 times daily (or 10 mg/kg is given 3 or 4 times daily). An administration rate of 100 mg/min should be used. Tranexamic acid is given by continuous infusion at a rate of 25 to 50 mg/kg daily.

When used in menorrhagia (p. 1165.1), a maximum dose of 4 g daily is given orally for up to 5 days during menstruation.

Tranexamic acid may also be given by slow intravenous injection in some cases of generalised bleeding. A dose of 10 mg/kg has been used for neutralisation of thrombolytic therapy. In disseminated intravascular coagulation, a single dose of 1 g may be sufficient to control bleeding (but see Precautions, p. 1165.2, regarding the safe use of tranexamic acid in this condition).

Tranexamic acid is used for prolonged periods in **hereditary angioedema** (p. 1165.1) in doses of 1 to 1.5 g given orally 2 or 3 times daily. It may be given intermittently or continuously, and the dose may be reduced to 500 mg once or twice daily as the attacks diminish. When used for short-term prophylaxis to prevent attacks related to surgery or dental work, a dose of 1 g may be given 4 times daily, for 48 hours before and after the procedure.

For doses used in children, see below.

Reduced doses are recommended for patients with renal impairment (see below).

Solutions of tranexamic acid have been applied topically, for example as a bladder irrigation or mouthwash.

Administration in children. Children may be given tranexamic acid in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. Usual doses of 15 to 25 mg/kg orally to a maximum of 1.5 g, or 10 mg/kg intravenously to a maximum of 1 g, are given 2 or 3 times daily. The *BNFC* also suggests that a dose of 45 mg/kg may be given by continuous intravenous infusion over 24 hours.

Similar doses have been used in the prophylaxis of hereditary angioedema. A consensus document[1] has recommended, as a general guide, an oral dose of 50 mg/kg daily (or 1 to 2 g daily) for long-term prophylaxis, but advised that the lowest effective maintenance dose should be used, and that alternate-day or twice-weekly regimens should be considered. For short-term prophylaxis, it suggested a dose of 500 mg given 4 times daily for 48 hours before and after surgery or dental procedures. A review[2] of paediatric treatment suggested an oral regimen of 20 to 40 mg/kg daily, to a maximum of 3 g, given in 2 or 3 divided doses, for long-term prophylaxis. This dose was also suggested for short-term prophylaxis before surgery, starting 5 days before the procedure and continuing for 2 days after. Prophylaxis for 2 or 3 days could be considered during infections, or when other precipitating factors are present.

1. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; 139: 379–94. Correction. *ibid.*; 141: 189–90. [close]
2. Farkas H, *et al.* Management of hereditary angioedema in pediatric patients. Abstract: *Pediatrics* 2007; 120: 635. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/3/e713 (accessed 21/12/09)

Administration in renal impairment. Licensed product information recommends reduced doses of tranexamic acid for patients with renal impairment, based on the serum-creatinine concentration (SCC):

- SCC 120 to 250 micromoles/litre: 15 mg/kg twice daily orally, or 10 mg/kg twice daily intravenously
- SCC 250 to 500 micromoles/litre: 15 mg/kg once daily orally, or 10 mg/kg once daily intravenously
- SCC higher than 500 micromoles/litre: 7.5 mg/kg once daily or 15 mg/kg once every 48 hours orally, or 5 mg/kg once daily or 10 mg/kg once every 48 hours intravenously (some products contra-indicate use in severe renal impairment)

Haemorrhagic disorders. Tranexamic acid and aminocaproic acid are structurally related synthetic antifibrinolytic drugs that block the binding of plasminogen and plasmin to fibrin, thereby preventing dissolution of the haemostatic plug.[1,2] A plasma concentration of tranexamic acid of 5 to 10 micrograms/mL has been considered necessary for effective inhibition of fibrinolysis.[2]

Antifibrinolytics are used to control haemorrhage that is considered to be caused by excessive fibrinolysis. Antifibrinolytic therapy may also be indicated in the prevention of rebleeding in some haemorrhagic conditions, the rationale being to retard dissolution of the haemostatic plug formed in response to vascular injury.

In haemorrhage caused by a congenital or acquired deficiency of blood coagulation factors, haemostatic drugs have a secondary role and may be useful in reducing requirements of factor concentrates. In patients with haemophilias (p. 1126.3) antifibrinolytics may be added to coagulation factor replacement before dental surgery, and used in the prevention and treatment of mucosal bleeding after the procedure. The route depends on the severity of the coagulation factor deficiency and the procedure to be undertaken; for example, tooth extraction will probably require more prophylactic cover than dental scaling. Regimens therefore vary,[3-7] but an initial oral or intravenous dose of tranexamic acid may be followed by oral use, or topical 5% mouthwash continued for up to 7 days after dental procedures. Tranexamic acid has been used similarly in patients with von Willebrand's disease[4] (p. 1129.3). An approach using tranexamic acid mouthwashes has also been used to reduce the risk of bleeding after oral surgery in patients on anticoagulant therapy.[8,9] Tranexamic acid may prove beneficial in patients with other congenital bleeding disorders such as α_2-antiplasmin deficiency.[10] Aminocaproic acid has been tried in a few patients with hereditary haemorrhagic telangiectasia with mixed results.[11] Tranexamic acid has been reported to be effective in the control of epistaxis in these patients; reports generally describe oral use,[12,13] but tranexamic acid has also been applied directly as nasal drops.[14]

Tranexamic acid or aminocaproic acid have been suggested to control bleeding in many other conditions. These include haemorrhage after surgical or other procedures including prostatectomy, bladder surgery, and cervical conisation. They may be used to reduce perioperative blood loss and allogeneic transfusion requirements.[15-19] They may also be effective in other conditions associated with excessive fibrinolysis such as menorrhagia (see p. 1165.1), epistaxis, and placental abruption. Tranexamic acid has also been found to reduce the risk of death in bleeding trauma patients, when given within 8 hours of injury.[20]

Tranexamic acid and aminocaproic acid have each been used in an attempt to prevent rebleeding in patients with subarachnoid haemorrhage (see Stroke, p. 1269.2), particularly if surgery is to be delayed. However, while rebleeding may be reduced, there can be an increase in the incidence of cerebral ischaemic complications resulting in little overall improvement in outcome.[21] Paradoxically, rebleeding has been noted in patients given high doses of aminocaproic acid after subarachnoid haemorrhage (see Effects on the Blood under Aminocaproic Acid, p. 1132.1).

Tranexamic acid has been used to control gastrointestinal haemorrhage, e.g. due to peptic ulcer disease (p. 1816.2) or oesophageal varices (see Variceal Haemorrhage under Monoethanolamine, p. 2563.1). In a meta-analysis[22] of 7 studies in patients with upper gastrointestinal haemorrhage, mortality was lower in those treated with tranexamic acid compared with placebo. However, there were no significant

differences in bleeding-related death, rebleeding or continued bleeding, surgery, or transfusion requirements. The management of upper gastrointestinal haemorrhage has changed significantly since some of the studies were undertaken, and tranexamic acid is not recommended for routine use in these patients.

1. Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998; 339: 245–53.
2. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs* 1999; 57: 1005–32.
3. Zanon E, *et al.* Proposal of a standard approach to dental extraction in haemophilia patients: a case-control study with good results. *Haemophilia* 2000; 6: 533–6.
4. Stubbs M, Lloyd J. A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B. *Aust Dent J* 2001; 46: 37–40.
5. Villar A, *et al.* The use of haemostatic drugs in haemophilia: desmopressin and antifibrinolytic agents. *Haemophilia* 2002; 8: 189–93.
6. Lee APH, *et al.* Effectiveness in controlling haemorrhage after dental scaling in people with haemophilia by using tranexamic acid mouthwash. *Br Dent J* 2005; 198: 33–8.
7. Scully C, *et al.* Oral care for people with hemophilia or a hereditary bleeding tendency, second edition (World Federation of Hemophilia, Treatment of Hemophilia series, April 2008, No 27). Available at: http://www.wfh.org/2/docs/Publications/Dental_Care/TOH-27_Oral-Care-Revised2008.pdf (accessed 09/12/09)
8. Carter G, Goss A. Tranexamic acid mouthwash—a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg* 2003; 32: 504–7.
9. Carter G, *et al.* Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg* 2003; 61: 1432–5.
10. Favier R, *et al.* Congenital α_2-plasmin inhibitor deficiencies: a review. *Br J Haematol* 2001; 114: 4–10.
11. Annichino-Bizzacchi JM, *et al.* Hereditary hemorrhagic telangiectasia response to aminocaproic acid treatment. *Thromb Res* 1999; 96: 73–6.
12. Sabbà C, *et al.* Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001; 345: 926.
13. Sabbà C, *et al.* Rendu-Osler-Weber disease: experience with 56 patients. *Ann Ital Med Int* 2002; 17: 173–9.
14. Klepfish A, *et al.* Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med* 2001; 161: 767.
15. Levi M, *et al.* Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; 354: 1940–7.
16. Schmarts. Antifibrinolytics. *Acta Anaesthesiol Belg* 2003; 54: 319–22.
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18. Brown JR, *et al.* Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; 115: 2801–13.
19. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
20. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; 376: 23–32.
21. Roos YB, *et al.* Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2003 (accessed 27/10/05).
22. Gluud LL, *et al.* Systematic review: tranexamic acid for upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2008; 27: 752–8.

Hereditary angioedema. Tranexamic acid is used as prophylactic therapy in the management of hereditary angioedema (p. 2485.2).

Menorrhagia. Tranexamic acid is used in women with menorrhagia (p. 2300.3) who do not require contraception or hormonal therapy. It reduces uterine blood loss in such women when used during menstruation.[1-3] A comparative study[1] found oral tranexamic acid 1 g every 6 hours to be more effective than the NSAID mefenamic acid, a commonly used treatment for the condition, and etamsylate. It is also more effective than cyclical norethisterone[2] (although less so than a progesterone-releasing intrauterine device[3]). A review,[4] which included these and some other studies, reported that tranexamic acid reduces menstrual blood loss by about 34 to 59% over 2 to 3 cycles.

1. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; 313: 579–82.
2. Preston JT, *et al.* Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; 102: 401–406.
3. Milsom I, *et al.* A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991; 164: 879–83.
4. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs* 2003; 63: 1417–33.

Adverse Effects

Tranexamic acid appears to be well tolerated. It can produce dose-related gastrointestinal disturbances. Hypotension and dizziness have occurred, particularly after rapid intravenous dosage. Thrombotic complications (including cerebral thrombosis and central retinal venous and arterial occlusion) have been reported in patients receiving tranexamic acid, but these are usually a consequence of its inappropriate use (see Precautions, below). Ocular and visual disturbances, including disturbance of colour vision, have been associated with use of tranexamic acid; in such cases the drug should be stopped. Other adverse effects that have been reported include hypersensitivity reactions, skin reactions, musculoskeletal pain, and convulsions.

Effects on the eyes. Tranexamic acid has been associated with retinopathy[1] and visual impairment.[2] A haemodialysis patient developed almost total loss of vision within 2 weeks of starting daily tranexamic acid injections after emergency surgery for a bleeding peptic ulcer. Vision was largely restored within a few days of stopping tranexamic acid,[2] although some impairment persisted in conditions of poor light. The patient had experienced visual impairment previously when given tranexamic acid. The authors noted that doses of tranexamic acid should be reduced in patients with renal impairment undergoing dialysis.

A patient undergoing regular peritoneal dialysis for Epstein's syndrome developed ligneous conjunctivitis, gingival hyperplasia, and peritoneal protein loss associated with the use of tranexamic acid.[3]

1. Snir M, *et al.* Central venous stasis retinopathy following the use of tranexamic acid. *Retina* 1990; 10: 181–4.
2. Kitamura H, *et al.* Tranexamic acid-induced visual impairment in a hemodialysis patient. *Clin Exp Nephrol* 2003; 7: 311–14.
3. Diamond JP, *et al.* Tranexamic acid-associated ligneous conjunctivitis with gingival and peritoneal lesions. *Br J Ophthalmol* 1991; 75: 753–4.

Effects on the skin. A widespread, patchy rash with associated blisters, considered on skin biopsy to be a fixed-drug eruption, occurred in a 33-year-old woman.[1] Tranexamic acid, which she had taken for 8 years and which had been well tolerated, was identified as the cause. Desensitisation was unsuccessful. Tranexamic acid was also suspected as being the cause of a fixed-drug eruption in a 36-year-old woman.[2] Pruritic, vesicle-bullous lesions appeared within a few hours of starting tranexamic acid and the lesions resolved completely 3 days after stopping therapy even though other drug treatment was continued.

1. Kavanagh GM, *et al.* Tranexamic acid (Cyklokapron)-induced fixed-drug eruption. *Br J Dermatol* 1993; 128: 229–30.
2. Carrión-Carrión C, *et al.* Bullous eruption induced by tranexamic acid. *Ann Pharmacother* 1994; 28: 1305–6.

Precautions

Tranexamic acid should not be used in patients with active intravascular clotting because of the risk of thrombosis. Patients with a history of, or predisposition to, thromboembolism are also at risk if given antifibrinolytic therapy. Haemorrhage due to disseminated intravascular coagulation should therefore not be treated with antifibrinolytic compounds unless the condition is mainly due to disturbances in fibrinolytic mechanisms; tranexamic acid has been used when the latter conditions are met, but with careful monitoring and anticoagulant cover.

Lysis of existing extravascular clots may be inhibited in patients receiving tranexamic acid. Patients with massive haematuria from the upper urinary tract may be at increased risk of ureteric obstruction. Doses of tranexamic acid should be reduced in patients with renal impairment. Licensed product information recommends that regular eye examinations and liver function tests should be performed if tranexamic acid is used long term.

Some studies have suggested that tranexamic acid when given to patients after a subarachnoid haemorrhage increases the incidence of cerebral ischaemic complications (see Haemorrhagic Disorders under Uses, p. 1164.3).

Rapid intravenous dosage may be associated with adverse effects (see above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tranexamic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Drugs with actions on haemostasis should be given with caution to patients on antifibrinolytic therapy. The risk of thrombosis may be increased if tranexamic acid is given with factor IX complex concentrates or factor VIII inhibitor bypassing fraction, and such combinations are not recommended. Antifibrinolytics and thrombolytics have antagonistic effects, and concomitant use may reduce the efficacy of both. The potential for thrombus formation may be increased by oestrogens.

Retinoids. Antifibrinolytics should be used with caution in patients receiving oral *tretinoin* as thrombotic events have been reported in patients being treated with tranexamic acid and tretinoin (see Antifibrinolytics, p. 1727.1).

Pharmacokinetics

Tranexamic acid is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 3 hours. Bioavailability is about 45%. Tranexamic acid is widely distributed throughout the body and has very low protein binding. It diffuses across the placenta and is distributed into breast milk. Tranexamic acid has a plasma elimination half-life of about 2 hours. It is excreted in the urine mainly as unchanged drug.

References.

1. Andersson L, *et al.* Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann N Y Acad Sci* 1968; 146: 642–56.
2. Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynecol Scand* 1970; 49: 241–2.
3. Pilbrant Å, *et al.* Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol* 1981; 20: 65–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tranexal; *Austral.*: Cyklokapron; *Austria*: Cyklokapron; *Belg.*: Exacyl; *Braz.*: Hemoblock; Transamin; Trexacont; *Canad.*: Cyklokapron; *Chile*: Espercil; *China*: Bei Rui Ning (贝瑞宁); Feimin (菲敏); He Mo Sai (荷莫塞); JieNing (捷凝); Jiening (捷宁); Ka Wei An (卡维安); Li Da Fei (力达非); Ta Jiu Shu (他久舒); Transamin (妥塞敏); *Cz.*: Exacyl; *Denm.*: Cyklokapron; Cyklonova; *Fin.*: Caprilon; Cyklokapron; *Fr.*: Exacyl; Spotof; *Ger.*: Cyklokapron; *Gr.*: Transamin; *Hong Kong*: CP-Tran; Cyklokapron†; Qualixamin; Tosano; Transamin; *Hung.*: Exacyl; *India*: Bio-Stat; Capitrax; Clip; Clotawin-T; Coastat; Cyklokapron; Cymin; Dubatran; Examic; Pegan; Gynae-Pil; Menogia; Mouzex; Nexim; Tranarest; Tranfib; *Indon.*: Asamnex; Clonex; Ditranex†; Ethinex; Intermic; Kalnex; Lunex; Nexa; Nexitra; Plasminex; Pytramic; Ronex; Theranex†; Tranec; Tranexid; Transamin; Tranxa; *Irl.*: Cyklokapron; *Israel*: Hexakapron; *Ital.*: Tranex; Ugurol; *Jpn*: Transamin; *Malaysia*: Transamin; Tren; *Neth.*: Cyklokapron; *Norw.*: Cyklokapron; *NZ*: Cyklokapron; *Philipp.*: Cyclotrax; Cyklokapron†; Dostan; Fibrinon; Fimoplas; Hemoclot; Hemostan; Hemostop; Hemotrex; Micranex; Pantrex; Proklot; Tarnex; Trenaxin; *Pol.*: Exacyl; *Rus.*: Tranexam (Транексам); *S.Afr.*: Cyklokapron; Tranic; *Singapore*: Cyklokapron; *Spain*: Amchafibrin; *Swed.*: Cyklo-F; Cyklokapron; Cyklonova; Tranon; *Switz.*: Cyklokapron; *Thai.*: Axamin; Falete; Tramic Transamin; Transic; Tranxamax; Tranxic; *Turk.*: Transamine; *UK*: Cyklo-F; Cyklokapron; Femstrual; *Ukr.*: Tranexam (Транексам); *USA*: Cyklokapron; Lysteda; *Venez.*: Ciclokapron.

Multi-ingredient Preparations. *Belg.*: Quixil†; *Denm.*: Quixil; *Fin.*: Quixil; *Fr.*: Quixil†; *Ger.*: Quixil†; *India*: Bio-Stat-MF; C-Sylate Plus; Capihem; Capitrax Plus; Chromostat; Clip-MF; Clotawin-T; Clotem Plus; Coag; Coastat Plus; Coastat-Gyne; Cosklot Plus; Cyclocos-TX; Cyclosym-TX; Dubatran-MF; Etam; Etex-T; Ethatol; ETM-T; Etosys-MF; Etosys; Examic-MF; Fenamic; Fetran-ES; Fetran-MF; Fibran Plus; Fibran-M; Florasyl-MF; Gynae-Pil Forte; Hamodam-M; Hamodam-T; Hemocrat; HMT; Klotinex; Meffnex; Mefitrax; Meflam; Mefnex; Mefsyn-TX; Meftal-TX; Meftrax; Menogia-MF; Menoguard; Menospan-MF; Menostat; Menotran; Mouzex-MF; No Blos For; Noblifen; Tranfib MF; *Ital.*: Quixil; *Jpn*: Sin Colgen Kowa Kaze†; *Neth.*: Quixil†; *Port.*: Quixil†; *Swed.*: Quixil†; *Switz.*: Quixil.

Pharmacopoeial Preparations

BP 2014: Tranexamic Acid Injection; Tranexamic Acid Mouthwash; Tranexamic Acid Tablets.

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von Willebrand Factor

Facteur Willebrand humain (human von Willebrand factor); Factor humanus von Willebrandi (human von Willebrand factor); Factor VIII-related Antigen; vWF; Фактор фон Виллебранда.

UNII — ZE22NE22F1 (von Willebrand factor human); 5T6B772R4Q (human coagulation factor viii/von Willebrand factor complex).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Human von Willebrand Factor). A sterile freeze-dried preparation of a plasma protein fraction that contains the glycoprotein von Willebrand factor with varying amounts of coagulation factor VIII, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors: the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

When reconstituted as stated on the label, the potency is not less than 20 international units of von Willebrand factor per mL. It is a white or pale yellow, hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

von Willebrand factor is used in the treatment and prophylaxis of bleeding in von Willebrand's disease (p. 1129.3), usually when desmopressin is ineffective or contra-indicated. It is generally contained in plasma concentrate preparations with factor VIII (p. 1148.1), but

highly purified preparations that contain very little factor VIII are also available in some countries. Dosage depends on the extent and source of bleeding. Hypersensitivity reactions may occur rarely, and as for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

References.
1. Smith MP, *et al.* Continuous infusion therapy with very high purity von Willebrand factor concentrate in patients with severe von Willebrand disease. *Blood Coag Fibrinol* 1997; 8: 6–12.
2. Goudemand J, *et al.* Clinical management of patients with von Willebrand's disease with a VHP vWF concentrate: the French experience. *Haemophilia* 1998; 4 (suppl 3): 48–52.
3. Carter NJ, Scott LJ. Human plasma von Willebrand factor/factor VIII complex (Haemate P/Humate-P): in von Willebrand disease and haemophilia A. *Drugs* 2007; 67: 1513–19.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies von Willebrand factor (when combined with factor VIII) as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Wilfactin; *Cz.*: Willfact; *Denm.*: Willfact; *Fin.*: Wilfactin; *Fr.*: Wilfactin; Wilstart; *Ger.*: Willfact; *Gr.*: Wilfactin; *Neth.*: Wilfactin; *Norw.*: Willfact; *Switz.*: Willfact.

Bone Modulating Drugs

The processes of bone turnover, and the regulation of body calcium, are intimately connected. The concentration of calcium in plasma is normally kept within a narrow range (p. 1777.3). It is regulated by the absorption and excretion of calcium, and also by modulation of the normal resorption and formation of bone and hence the movement of calcium to and from the skeletal reservoir. The endogenous substances parathyroid hormone, calcitonin, and vitamin D, are involved in the regulation of calcium homoeostasis.

Drugs described in this chapter affect bone resorption or formation, with effects on serum calcium. They include:

- bisphosphonates
- bone morphogenetic proteins
- calcitonins
- cinacalcet hydrochloride
- gallium nitrate
- parathyroid hormone
- strontium ranelate
- teriparatide

The inorganic fluoride salts, which can promote bone formation when given in appropriate doses, are discussed in the chapter on Nutritional Agents (see Sodium Fluoride, p. 2089.2).

Bone and Bone Disease

The skeleton acts as mechanical support and protection to softer tissues and organs. It is also important in electrolyte homoeostasis, acting as a reservoir of certain ions and minerals such as calcium, phosphorus, and magnesium.

Bone has two components: an organic matrix, called **osteoid**, consisting mainly of collagen, and a mineral phase deposited through that matrix; the latter, comprising about 70% of the skeletal mass, is composed chiefly of **hydroxyapatite** (a complex crystalline salt of calcium and phosphate). There are two structural forms known in mature bone:

- cortical (lamellar) bone, which has a dense, continuous structure
- trabecular (cancellous) bone, which has a 'spongy' structure of linked plates and is associated with high bone turnover and growth.

The peripheral or appendicular parts of the skeleton are mainly cortical bone, while the axial or central parts, such as the spine and pelvis, contain substantial amounts of trabecular bone.

Bone is a dynamic tissue: once new bone has been laid down it is subject to a continual process of formation and resorption called **remodelling**. Remodelling takes place along bone surfaces and is carried out by bone cells (osteoclasts and osteoblasts) that originate in the marrow and share common origins with blood cells. Stimulated by physical or chemical signals, **osteoclasts** dig a cavity into the bone (bone resorption); they are then replaced by ***osteoblasts*** *that synthesise new osteoid to fill the cavity* (bone formation) and may help to promote its subsequent mineralisation. The actions of these two types of bone cell are closely linked, and agents that suppress resorption ultimately decrease bone formation too. However, at any given time there is a deficit in potential bone mass, the **remodelling space**, which represents sites of bone resorption that have not yet been filled in. Any stimulus that affects bone turnover by altering the recruitment of osteoblasts and osteoclasts to remodelling will result in an increase or decrease in the remodelling space, until a new steady state is achieved, and this will be seen as a decrease or increase in bone mass. Lifelong accumulation of remodelling deficits leads to age-related bone loss.

Bone also contains **osteocytes**, which are cells derived from osteoblasts thought to be involved in the movement of minerals.

Bone cells are controlled by systemic hormones including parathyroid hormone, 1,25-dihydroxycholecalciferol (calcitriol), calcitonin, and local regulators such as bone morphogenetic proteins and cytokines. A local signalling system involving the protein RANKL (receptor activator of nuclear factor-kappa B ligand), which induces osteoclast differentiation and activation and promotes bone resorption, and the protein osteoprotegerin, which inhibits osteoclast formation and prevents bone resorption, is mediated via the receptor RANK found on osteoclasts and their precursors.

Bone diseases may be due to defects in the production of osteoid or its mineralisation, or to an imbalance in resorption and formation of bone. Bone balance can be affected by diverse stimuli such as dietary insufficiency, hormones, including sex hormones, and drugs such as corticosteroids.

Hypercalcaemia of malignancy

About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive.[1,2] The condition is thought to be mediated usually by parathyroid hormone-related protein released from tumour tissue, which acts both locally and systemically to enhance osteoclastic bone resorption and increase renal tubular calcium reabsorption. Increased levels of parathyroid hormone-related protein have been found in hypercalcaemic patients, especially those with solid tumours, regardless of the existence of bone metastases.[3,4] Other causes of hypercalcaemia of malignancy include the activation of osteoclasts by the local release of bone-resorbing cytokines such as interleukin-1, interleukin-6, tumour necrosis factors, and growth factors;[3,4] this mechanism occurs particularly in those with myeloma.[4] The RANKL signalling system may play an important role.[5] Some lymphomas secrete active vitamin D, enhancing osteoclastic bone resorption and intestinal calcium absorption. Rarely, ectopic secretion of parathyroid hormone may cause hypercalcaemia.[6]

Bisphosphonates are the preferred drugs for **treating** hypercalcaemia once the patient has been adequately rehydrated with intravenous sodium chloride 0.9% (see Hypercalcaemia, p. 1778.1). It has been recommended[6] that therapy be begun as soon as possible, since a response is only seen after 2 to 4 days; in about 60 to 90% of patients serum calcium concentrations normalise within 4 to 7 days, and responses last for up to 3 weeks.[6] There is some evidence that bisphosphonates may be less effective in patients with high initial levels of parathyroid hormone-related protein; in addition, they have no effect on the renal tubular resorption of calcium.[2] There is no consensus as to the best bisphosphonate to choose. Pamidronate has been widely used and is considered by many to be the drug of choice.[7] A systematic review,[2] which noted that aminobisphosphonates were most effective in this condition, considered low-dose clodronate less effective than pamidronate although no difference was seen at higher doses. Others have queried the existence of a dose response for clodronate;[1] the fact it can be given subcutaneously, or orally (after intravenous therapy) may be useful.[1,4] Etidronate, which can also be given orally, is also less effective than pamidronate,[7,8] and prolonged therapy may cause osteomalacia. Alendronate has been found to be as effective as clodronate, and superior to etidronate.[2] Studies with neridronate and risedronate have been more limited;[1] incadronate has also been used.[2] However, newer aminobisphosphonates such as ibandronate and zoledronate may be the most effective option, with longer durations of response and more convenient dosage than pamidronate.[1,4] In patients unresponsive to low initial doses of bisphosphonates, some recommend larger doses;[6] alternatively, other drugs may be considered.

Calcitonin has a rapid onset of action, and is particularly useful in life-threatening hypercalcaemia.[1,7] This effect, however, is short-lived, and calcitonin is generally used as adjunctive therapy.[1] When given with bisphosphonates, calcitonin reduces serum calcium more rapidly than bisphosphonates given alone.[4]

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, has been used to obtain a rapid (within 24 hours) and sustained reduction in plasma-calcium concentrations in severe hypercalcaemia. However, it is highly toxic and its use no longer recommended.[1,5] *Gallium nitrate* also inhibits bone resorption; initial studies in patients with hypercalcaemia associated with malignancy have indicated beneficial effects,[3] but bisphosphonates are still likely to be preferred.[4,5]

Corticosteroids are useful in hypercalcaemia associated with corticosteroid-sensitive haematological malignancies such as lymphoma or myeloma.[1,4,6] In addition they may be useful to overcome renal tubular resistance to calcitonin[9] but otherwise are not usually effective.[10] There have been individual reports of beneficial results using somatostatin analogues such as *octreotide* for the treatment of hypercalcaemia of malignancy.

1. Body J-J. Hypercalcemia of malignancy. *Semin Nephrol* 2004; **24**: 48–54.
2. Saunders Y, *et al.* Systematic review of bisphosphonates for hypercalcaemia of malignancy. *Palliat Med* 2004; **18**: 418–31.
3. Leyland-Jones B. Treatment of cancer-related hypercalcemia: the role of gallium nitrate. *Semin Oncol* 2003; **30** (suppl): 13–19.
4. Ralston SH, *et al.* Medical management of hypercalcemia. *Calcif Tissue Int* 2004; **74**: 1–11.
5. Lumachi F, *et al.* Medical treatment of malignancy-associated hypercalcemia. *Curr Med Chem* 2008; **15**: 415–21.
6. Stewart AF. Hypercalcemia associated with cancer. *N Engl J Med* 2005; **352**: 373–9.
7. Davidson TG. Conventional treatment of hypercalcemia of malignancy. *Am J Health-Syst Pharm* 2001; **58** (suppl 3): S8–S15.
8. Berenson JR. Treatment of hypercalcemia of malignancy with bisphosphonates. *Semin Oncol* 2002; **29** (suppl 21): 12–18.
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Malignant neoplasms

The bisphosphonates and calcitonins are used to control the hypercalcaemia that often accompanies malignant disease (see above). Bisphosphonates are also used in metastatic bone disease (p. 700.3) to control bone pain and to reduce skeletal complications such as fractures. Evidence of the ability of bisphosphonates to prevent the development of bone metastases is conflicting. Bisphosphonates have been found to be effective in reducing the skeletal complications of multiple myeloma (p. 699.2) and are recommended in those patients with bone disease. Denosumab is also under investigation in the prevention of the development of bone metastases.

Osteogenesis imperfecta

Osteogenesis imperfecta (brittle bone syndrome) is a heterogeneous inherited disorder of connective tissue characterised by bone fragility, osteopenia, short stature, joint laxity, teeth defects, and hearing abnormalities.[1,2] It is often classified into 4 forms, I-IV, which vary in clinical severity, and radiological and genetic aspects;[1] some distinguish 3 further forms, V, VI, and VII.[2]

Orthopaedic treatment and physical activity programmes form the basis of **therapy**: at present there is no curative drug therapy.[1-3] *Calcitonins* were commonly used in management, but their use has declined.[1] Beneficial effects have been reported with growth hormone, especially in moderate forms of the disease.[1] *Bisphosphonates* have been found useful in osteogenesis imperfecta,[3,4] particularly in severe disease.[1] It is generally agreed that they improve bone mineral density,[3-5] and commentators have suggested that this is associated with improvements in chronic pain, fracture rate, and mobility,[3,4] although a systematic review considered that these benefits, as well as long-term safety (particularly in children) had not yet been adequately demonstrated.[5] Cyclic intravenous pamidronate has been the most widely used bisphosphonate, but benefit has also been reported with intermittent intravenous neridronate,[6,7] as well as daily oral clodronate.[8] Alendronate and zoledronate are under investigation.[4] Bisphosphonates may also be useful for associated immobilisation hypercalcaemia.[9] Immobilisation can also result in calcium and vitamin D deficiency, and prophylactic supplementation may be useful.[3] Bone marrow transplantation and the potential of antisense gene therapy are being investigated.[1,2]

1. Antoniazzi F, *et al.* Osteogenesis imperfecta: practical treatment guidelines. *Pediatr Drugs* 2000; **2**: 465–88.
2. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet* 2004; **363**: 1377–85.
3. Chevrel G, Meunier PJ. Osteogenesis imperfecta: lifelong management is imperative and feasible. *Joint Bone Spine* 2001; **68**: 125–9.
4. Devogelaer J-P. New uses of bisphosphonates: osteogenesis imperfecta. *Curr Opin Pharmacol* 2002; **2**: 748–53.
5. Phillipi CA, *et al.* Bisphosphonate therapy for osteogenesis imperfecta. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 21/01/09).
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8. Ashford RU, *et al.* Oral clodronate as treatment of osteogenesis imperfecta. *Arch Dis Child* 2003; **88**: 945.
9. Williams CJC, *et al.* Hypercalcaemia in osteogenesis imperfecta treated with pamidronate. *Arch Dis Child* 1997; **76**: 169–70.

The symbol † denotes a preparation no longer actively marketed

Osteomalacia and rickets

Osteomalacia occurs in adults when there is impaired mineralisation of the bone matrix, and rickets occurs in children due to defective mineralisation of the cartilaginous growth plate.[1-3] Generally the inadequate bone mineralisation results from deficiency or abnormal metabolism of vitamin D,[1,2,4] calcium deficiency,[1,3] or phosphate deficiency or depletion.[1-3] Several hereditary disorders are associated with the development of rickets including vitamin D-pseudodeficiency rickets (vitamin D-dependent rickets), in which there is impaired synthesis of 1,25-dihydroxycholecalciferol (Type I) or receptor resistance to 1,25-dihydroxycholecalciferol (Type II), and X-linked hypophosphataemic rickets.[2,6] Osteomalacia also occurs in renal osteodystrophy[2] associated with chronic renal failure (see p. 1170.1). Oncogenic osteomalacia is a rare form characterised by hypophosphataemia and renal phosphate wasting caused by a tumour, usually mesenchymal.[2,3] Some drugs including various antiepileptics (p. 540.2), etidronate, and aluminium salts, can interfere with bone mineralisation and cause osteomalacia. Osteomalacia may present with generalised or local bone pain, polyarthralgias, or muscle weakness.[2] Rickets characteristically causes skeletal deformities, epiphyseal enlargement, muscle hypotonia, and teeth defects.[1-4,6]

Treatment of osteomalacia and rickets is mainly aimed at correcting any underlying deficiency.[2] Vitamin D substances, calcium, or phosphate supplements can be given orally as appropriate but doses require careful individual adjustment to maintain calcium and phosphate concentrations within normal limits.[2,5] Vitamin D requirements are probably greater in those with reduced calcium intake, and calcium requirements greater in those with limited sunlight exposure and dietary vitamin D intake.[5]

A variety of forms or analogues of vitamin D are available (see p. 2112.3). For the treatment of simple vitamin D deficiency colecalciferol or ergocalciferol are generally preferred.[4] If malabsorption is suspected, larger doses or parenteral use may be necessary, but where large doses are required it may be preferable to use one of the more potent forms of vitamin D such as calcitriol.[2]

Simple calcium deficiency may be a more important cause of rickets than vitamin D deficiency in some populations. A study in African children with rickets found that their calcium intake was low and that they responded better to calcium supplementation, with or without vitamin D, than to vitamin D alone.[5]

Type I vitamin D-pseudodeficiency rickets requires replacement therapy with calcitriol. In Type II disease, resistance to calcitriol treatment may be so extreme that only very large supplements of calcium may be effective. X-linked hypophosphataemic rickets is considered to be best treated with combined phosphate supplementation and calcitriol.[3] There has also been some interest in the use of growth hormone in children with hypophosphataemic rickets.[7] A form of hypophosphataemic rickets, rickets of prematurity (see under Osteomalacia, p. 1794.1), may occur in small, premature infants fed exclusively on breast milk, and phosphate supplementation plus calcium and vitamin D has been suggested in such cases. Prophylaxis of calcium or vitamin D deficiencies through adequate dietary intake or supplementation is controversial given difficulties in deciding definitive requirements (see Human Requirements under Calcium, p. 1788.2, and Human Requirements, p. 2118.1, and Osteomalacia, p. 2116.2, under vitamin D).

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Osteoporosis

Osteoporosis is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and risk of fracture, particularly of the long bones (distal forearm and neck of the femur) and the vertebrae.[1-9] Although bone formation outstrips resorption in youth, accumulated small deficits from remodelling (see Bone and Bone Disease, p. 1167.1) result in a gradual loss of bone mass after the third or fourth decades.[2-4,6,10] Primary osteoporosis is therefore usually an age-related disease. It can affect both sexes, though women are at greater risk because bone loss is accelerated, to a variable degree, after the menopause.[1-3,5,6,10,11] Osteoporosis can also be secondary to chronic endocrine or metabolic conditions[1,5,6,10-12] such as hyperparathyroidism (p. 1170.3), hyperthyroidism (p. 2332.2), diabetes mellitus (p. 458.2), Cushing's syndrome (p. 2559.1), malabsorption syndromes, anorexia nervosa, or inflammatory bowel disease (p. 1811.3) affecting calcium and vitamin D absorption. Other conditions associated with bone loss and osteoporosis include osteogenesis imperfecta (p. 1167.3), rheumatoid arthritis (p. 13.2), complex regional pain syndrome (p. 8.1), chronic renal disease, multiple myeloma (p. 699.2), and HIV (p. 958.3); osteoporosis may also follow organ and tissue transplantation or prolonged immobilisation. Other secondary causes include the use of drugs[1,5,6,10,11,13,14] such as corticosteroids (p. 1616.2), thyroid hormones, anticonvulsants, gonadorelin analogues (p. 2282.1), aromatase inhibitors, and heparin (p. 1399.2).

Risk factors for osteoporosis include non-modifiable predictors of low bone mineral density (BMD), such as female sex, increased age, Caucasian or Asian race, while other factors are potentially modifiable but may be independent of BMD, such as cigarette smoking, alcohol consumption, low body-weight, and physical inactivity. Other factors include early menopause, hypogonadism, including prolonged amenorrhoea in women, high caffeine intake, and nutritional deficiencies such as low calcium intake and vitamin D deficiency.[1,3,6,10,13,15,16] The most important risk factors for osteoporosis-related fracture are a history of low-trauma fracture as an adult (40 years of age or older) and low BMD.[1,3,4] For men, important risk factors include increasing age (over 70 years) and low body-weight (BMI of less than 20 kg/m^2).[16]

Patients are usually asymptomatic until fractures occur,[6,15] and up to two-thirds of vertebral fractures may also be asymptomatic.[1,6] Fractures can result in pain, deformity (kyphosis, loss of height), and disability.[1] Currently, the most reliable method of **assessment** for osteoporosis and fracture risk is measurement of BMD, usually by dual energy X-ray absorptiometry.[1,3,4,6,17] WHO have defined osteoporosis as a BMD 2.5 standard deviations or more below the young adult mean, and severe or established osteoporosis as this BMD in the presence of one or more fragility fractures.[3] There is no universally agreed policy on screening for osteoporosis, but measurement of BMD should be considered in those thought to be at risk of osteoporosis if the result is likely to affect treatment decisions.[2,3,7,10,18,19]

Since osteoporosis is defined in terms of BMD, the distinction between clinical consequences, such as fractures, and risk, is blurred. Thus, differences between prevention and treatment are increasingly difficult to define; objectives are similar and interventions the same.[3] Goals in **management** are to prevent fractures, optimise skeletal development to maximise peak BMD at skeletal maturity, stabilise BMD and prevent bone loss, preserve structural skeletal integrity, decrease morbidity and mortality from fractures, and to relieve symptoms of fractures and skeletal deformity.[1,4] Secondary causes of osteoporosis should be identified and treated as appropriate.[4]

General **non-pharmacological** measures include:

- ensuring adequate dietary calcium and vitamin D intake (see under Human Requirements, p. 1788.2 and p. 2118.1), especially during growth.[1,3,4,20,21] Supplementation may be necessary, see below.
- regular weight-bearing exercise; during growth this optimises peak bone mass,[3,4,19-21] but is also beneficial in pre-and postmenopausal women in terms of increasing BMD and reducing the risk of fractures.[1,4,19,22] However, exercise does not appear to prevent fractures in postmenopausal women during the first 2 years of exercise.[23]
- lifestyle modifications such as smoking cessation (p. 2570.2) and moderation of caffeine and alcohol intake.[1,3,4,9,21,22]
- interventions to reduce or prevent falls and injuries; measures to protect the patient should falls occur may also be considered.[1,4,19,21,22]
- Supportive therapy in the acute phase of a fracture, including pain relief, surgery or appropriate orthopaedic management.[20]

Pharmacological treatment aims to increase bone mass, either by inhibiting bone resorption, or by stimulating bone formation through anabolic effects.[1,24] While many drugs are used, not all have been well evaluated for their effect on fracture rates, and there are few comparisons.[25] Furthermore, many studies have been conducted in postmenopausal osteoporotic women, and evaluation in postmenopausal women with normal BMD, osteopenic women with no fracture, or men, is limited.[3,19]

- Calcium and vitamin D supplementation is accepted baseline adjunctive treatment for osteoporosis and may also be used as a prophylactic measure.[4,7,20,24] Calcium supplementation has a small but positive effect on BMD and tends to reduce the incidence of vertebral fractures. Low vitamin D status has been associated with reduced BMD, and increased risk of falls and hip fracture in elderly people; however, differences in baseline vitamin D concentrations make comparison of studies difficult.[8] Vitamin D supplementation appears to reduce the risk of hip and non-vertebral fractures,[7,8] especially in those with vitamin D deficiency. Excessive vitamin D should be avoided, as this may decrease BMD.[2] Studies of supplementation with calcium plus vitamin D show equivocal results on fracture rates.[8] However, daily calcium with vitamin D supplementation is recommended for elderly institutionalised people with limited exposure to sunlight.[18,19,22]
- Bisphosphonates are antiresorptive drugs that are used first-line for the treatment and prevention of osteoporosis.[4,18,19,21] While aminobisphosphonates and non-nitrogen-containing bisphosphonates differ in their effect on BMD,[17,26] no comparative studies have been done and BMD changes do not necessarily correlate with fracture reduction;[26] some consider effect on fracture rates to be similar.[17]
  There is good evidence that alendronate, risedronate, or zoledronate can prevent bone loss,[4,11] improve BMD[1,4,6] and reduce the risk of both vertebral and non-vertebral fractures.[1,2,4,8,9,15,24] These effects are seen within 1 year of starting treatment,[27] and effects on BMD persist for some while after stopping the drug, particularly with alendronate.[17] Evidence for other bisphosphonate is more patchy: oral or intravenous ibandronate,[11] and intravenous pamidronate[6] have been shown to increase BMD at the spine and hip. Oral ibandronate has been shown to decrease vertebral fracture risk in women with osteoporosis, as well as non-vertebral fracture risk in those with severe disease.[11,28] Intravenous ibandronate has been associated with a reduction in the incidence of new fractures.[11] Oral cyclical etidronate has been shown to decrease the risk of vertebral fractures,[1,3] (as has oral clodronate[20]), but evidence for an effect on non-vertebral fractures is less clear.[20] In the UK, NICE recommends[29] alendronate for the primary prevention of osteoporotic fragility fractures in postmenopausal women with confirmed osteoporosis; those below 65 years must have an independent clinical risk factor or fracture and at least one additional indicator of low BMD, women aged 65 to 69 years must have an independent clinical risk factor for fracture, and women aged 70 years or older must have an independent clinical risk factor or fracture or an indicator of low BMD. Risedronate and etidronate are recommended as alternatives in high-risk women unable to take alendronate. NICE also recommends[30] alendronate for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with confirmed osteoporosis who have sustained a clinically apparent fracture; risedronate and etidronate are alternatives in high-risk women unable to take alendronate.
- In postmenopausal women, HRT (p. 2245.1) was initially considered first-line,[31] as its antiresorptive action has been shown to preserve BMD and decrease hip and vertebral fracture risk.[1,2,24] However, results from the Women's Health Initiative and Million Women studies suggested that long-term use of HRT could increase the risk of breast and some other cancers (see p. 2246.3), while not reducing cardiovascular risk or improving cognitive function. The UK CSM has thus recommended that HRT no longer be considered as a first-line therapy for the prevention of osteoporosis in women aged over 50 years and at increased risk of fractures;[32] it remains an option for those intolerant of or refractory to other therapies, and for prevention of osteoporosis in women with premature menopause until the age of 50. It has been suggested that treatment not exceed 5 years,[4] although others suggest treatment of 7 to 10 years in order to maximise effect in those women considered at greater benefit than risk with HRT.[2] A large study found that women who had stopped using HRT more than 5 years previously had similar hip fracture risk to those who had never used HRT. However, those who had stopped using HRT within the previous 5 years had a higher risk of hip fracture than in those who had never taken HRT.[33]
- Raloxifene is a selective oestrogen receptor modulator (SERM) that partially mimics the effects of oestrogen in bone and the cardiovascular system, but without the stimulatory effects on the endometrium and breast.[3] Raloxifene significantly increases BMD in postmenopausal women and reduces vertebral fracture risk in those women with osteoporosis,[4,21,34] although it may exacerbate cardiovascular problems.[11,18] Risk of non-vertebral fracture is not affected,[3,18] and some consider SERMs less effective than the bisphosphonates.[11] NICE recommends[30] raloxifene for the secondary prevention of osteoporotic fragility fractures in high-risk women unable to take bisphosphonates. It is not recommended for primary prevention in postmenopausal women.[29]
- Combination therapy of HRT or raloxifene with bisphosphonates has increased BMD but with no effects on fracture reduction.[20]
- Strontium ranelate has both anabolic and resorptive properties.[20] It has been found to increase BMD at the spine and hip, and reduce new vertebral, non-vertebral, and hip fractures in postmenopausal women with

osteoporosis.[9,11] NICE recommends strontium ranelate for the primary[29] and secondary[30] prevention of osteoporotic fragility fractures in high-risk postmenopausal women unable to take bisphosphonates.

- Parathyroid hormone and its analogue teriparatide also have anabolic effects on bone, and increase BMD at the spine.[21,24] Daily subcutaneous injections of teriparatide reduced the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis.[4,35] Teriparatide has also been shown to increase lumbar and femoral BMD, and reduce non-vertebral fractures to a greater extent than alendronate.[5] The response to parathyroid hormone may be modified by previous or concurrent treatment with antiresorptive drugs.[6] NICE recommends[30] teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women who have had an unsatisfactory response to bisphosphonates or who are unable to take bisphosphonates or strontium ranelate; women aged 65 years or older must have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3.5 standard deviations or more below the mean) plus more than 2 fractures, and women aged 55 to 64 must have an extremely low BMD plus more than 2 fractures.
- Calcitonins are antiresorptive agents with an adjunctive or second-line role in the treatment of osteoporosis; calcitonin (salmon) is given by subcutaneous injection or intranasally as a spray. Both routes have been found to increase spinal BMD;[1,4,5] decreases in vertebral[4,31] fracture risk have been seen with the nasal spray, although the beneficial effect on nonvertebral fracture may be less than with bisphosphonates.[36] A review by the EMEA found an increased risk of cancer with long-term use of calcitonins and subsequently recommended against their use in postmenopausal osteoporosis (for further details see Carcinogenicity, under Adverse Effects, Treatment, and Precautions of Calcitonins, p. 1179.2); however, such use may still be permitted in other countries. It has been suggested that the analgesic effects of calcitonins may be valuable in patients with acute pain due to osteoporotic fractures,[2,3,18,24] the analgesia being achieved within 2 weeks,[6] although some would only recommend it for pain from acute vertebral compression fractures.[21]
- Denosumab is a monoclonal antibody that reversibly inhibits osteoclast-mediated bone resorption. It has been shown to improve bone mineral density and reduce the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis,[4] and may be considered first-line therapy for women who cannot take bisphosphonates.[37] It is also used for osteoporosis in men and bone loss associated with some hormonal treatments for cancer.
- Tibolone is a synthetic steroid with combined oestrogenic, progestogenic, and androgenic properties, that increases BMD comparably to HRT, relieves vasomotor symptoms, and does not cause endometrial proliferation.[3] However, there are limited data on fracture prevention, and some do not recommend its use for treatment of osteoporosis.[24] A large study[38] of the treatment of osteoporosis in postmenopausal women aged between 60 and 85 years was stopped early when it was found that although tibolone reduced the risk of fracture, breast cancer, and possibly colon cancer, there was an increased risk of stroke. The authors therefore concluded that tibolone should not be used in elderly women and women with risk factors for stroke.
- Anabolic steroids such as nandrolone have been found to increase BMD similarly to HRT, but adverse effects and limited data on fracture reduction efficacy have limited their use.[3,19]
- Fluoride has a direct anabolic effect on the osteoblast, stimulating bone formation; it has been given as sodium fluoride or sodium monofluorophosphate in the treatment of osteoporosis.[3] However, increases in lumbar BMD with fluoride have not resulted in decreased vertebral fracture rate, and may even be associated with increased bone fragility and an increase in non-vertebral fractures.[3,39] Thus fluoride is not widely recommended for osteoporosis management; fluoride water concentrations should be taken into account if it is used.[3]
- There is some suggestion that HMG-CoA reductase inhibitors (statins) can stimulate bone formation and have the potential to reduce fracture risk, but data are conflicting, and further studies are needed.[40,41]
- Thiazide diuretics reduce urinary calcium excretion and observational studies have found patients to have a higher BMD and fewer hip fractures;[3] however, effects are small and therapy is likely to be restricted to an adjunctive preventative role.[1,3,5]
- Ipriflavone is a synthetic isoflavone that may inhibit bone resorption; results on BMD from trials are conflicting, and data on fracture reduction lacking.[1,3]
- Vitamin K plays a role in bone metabolism, and is licensed in some countries in the management of osteoporosis; it has been suggested that vitamin K substances should be given to patients at risk of reduced bone mineralisation.[42] A systematic review and meta-analysis found that vitamin K supplementation was associated with increased BMD and a reduced fracture incidence, especially of the hip;[43] however, routine supplementation is not considered justified until these results are confirmed in a large randomised study with fractures as primary outcome.
- Potential anabolic agents in the management of osteoporosis include growth hormone and insulin-like growth factor I.[5,35] Novel antiresorptive agents under investigation include cathepsin K inhibitors,[44] cytokine inhibitors,[5,24] and osteoprotegerin.[5,45]

There is less evidence to guide decisions on the management of osteoporosis in men[3,46] than in postmenopausal women. Calcium and vitamin D intake or supplementation, nutritional and lifestyle advice are similar to that for women.[46-48] In hypogonadal men with osteoporosis, testosterone replacement therapy should be used.[3,46,47] In eugonadal men, there are concerns regarding the potential long-term adverse effects of exogenous testosterone.[46,48] Therefore, in men with idiopathic osteoporosis, bisphosphonates may be the treatment of choice.[47] Alendronate has been found to increase BMD at all sites and decrease vertebral fracture rates in men with osteoporosis,[47] and there have been some reports of beneficial effects on lumbar BMD have been reported with cyclical etidronate. Preliminary results with risedronate indicate favourable increases in lumbar BMD and a decrease in vertebral fracture risk.[46]

Beneficial effects on both lumbar and femoral BMD have been reported with teriparatide; its effect on BMD when used alone was found to be greater than when used with alendronate, or that of alendronate alone.[47] After teriparatide is stopped, treatment with a bisphosphonate is recommended to further increase BMD.[13] While efficacy in fracture prevention is lacking, teriparatide may be considered second-line for patients unable to take bisphosphonates.[46] Nasal calcitonin (salmon) has been found to increase lumbar BMD in men with idiopathic osteoporosis,[47] but most similarly reserve its use for those who cannot tolerate bisphosphonates.[46,48]

Of the other available drugs, fluoride has increased BMD and decreased vertebral but not non-vertebral fractures.[47] Thiazide diuretics have been reported to be of benefit, but data on BMD and fracture risk are conflicting; they may be given as adjunctive therapy in men with hypercalciuria.[46] Use of growth hormone in men with idiopathic osteoporosis led to gains in BMD in a small uncontrolled study.[48]

In **children**, calcium and vitamin D supplements are considered appropriate for low BMD.[49] Although there are only limited data in children, bisphosphonates (particularly pamidronate) have been used for both prevention and treatment. In children who have osteoporotic fractures, increases in BMD, reductions in fracture frequency, and relief of pain have been reported after bisphosphonate use.

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Paget's disease of bone

Paget's disease of bone (osteitis deformans) is a progressive bone disease of unknown aetiology, characterised by excessive and disorganised bone resorption and formation.[1-4] It may affect single (monostotic) or multiple bones (polyostotic);[1,2,5] the most commonly affected bones include the pelvis, femur, lumbar spine, skull, and tibia.[1,2,4,5] It affects 1 to 2% of white adults older than 55 years[1] and its frequency increases with age,[1,2] although there are large ethnic and geographical differences in incidence.[1] Patients may be asymptomatic, but some present with musculoskeletal and bone pain, or with bone weakness and deformity that can result in fractures.[2-4,6] Other complications include hearing loss, osteoarthritis, spinal stenosis, nerve compression (especially of the spinal cord), cranial nerve palsies, and rarely, hydrocephalus or brainstem compression. Cardiac output increases due to increased skeletal vascularity, but high-output heart failure is rare, as is malignant transformation to osteosarcoma.[2-4]

Patients who are asymptomatic may require no **treatment**;[3,7] however treatment is warranted, in those patients with biochemical markers of active disease or in whom the sites of disease are associated with a risk of progression and future complications.[4,7] Drug therapy is guided by monitoring biochemical improvement in disease activity.[2,8]

Bone pain may be treated with *analgesics* or *NSAIDs*, or with drugs that reduce bone resorption, such as the calcitonins and bisphosphonates.[2,4,5]

Bisphosphonates are indicated for persistent bone pain, or to prevent further progression of the disease, especially if

complications such as spinal-cord compression are present or there is a risk of such complications.[3,7] Disease activity may be reduced for several months, or years, after bisphosphonate therapy has ceased.[7] However, while bone turnover is suppressed, and osteolytic lesions may be healed, the underlying disorder is not cured; data on long-term effects of bisphosphonates on fractures, bone deformity, or osteoarthritis are limited and they may theoretically exacerbate hearing loss.[2]

Initial experience was with etidronate,[7,8] but it is less effective than the newer drugs, and with high doses or prolonged treatment can affect bone mineralisation;[4,7,8] while some still consider it effective,[7] others consider it to have little place in the management of Paget's disease.[3,8,9] Clodronate appears to provide a higher and more sustained response than etidronate.[7] Pamidronate, more effective at healing lesions than etidronate, also gives a prolonged response, although its effects may diminish due to resistance.[7] Alendronate or risedronate both reduce biochemical markers of disease activity with sustained remission,[4,7,9] are more effective than etidronate,[9] and overcome resistance to pamidronate;[3] risedronate may be useful after incomplete response to etidronate.[7] Tiludronate is also more effective than etidronate, with no effect on bone mineralisation, no reported resistance,[7] and may be a viable option for those patients unable to tolerate other bisphosphonates.[4] Neridronate has been reported to be beneficial in those patients with resistance to etidronate and clodronate.[7] Preliminary studies indicate suppression of disease activity with ibandronate.[8] Zoledronate has shown benefit in refractory disease, and some suggest that it should be a first-line option.[6]

Bisphosphonates have superseded *calcitonins*,[3,5,7,8] which have a short-lived effect and which generally are less effective in suppressing bone turnover and improving bone pain.[2] Calcitonins may still have a role in those patients for whom bisphosphonates are intolerable or ineffective;[5,8] however, resistance to both bisphosphonates and calcitonins may occur,[4] and long-term use of calcitonins has been associated with an increased risk of cancer (for details see Carcinogenicity, under Adverse Effects, Treatment, and Precautions of Calcitonins, p. 1179.2).

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, is highly effective in the treatment of Paget's disease of bone.[7] However, it is associated with severe toxicity and is therefore now avoided or reserved for patients refractory to other drugs.[4,7,8]

Studies with *gallium nitrate*, another inhibitor of bone resorption, have indicated beneficial effects in the treatment of Paget's disease of bone, but long-term haematological safety has not been established,[7] and routine use is not recommended.[8] *Ipriflavone* has also been reported to be of benefit, but remains investigational for Paget's disease.[7]

In selected patients, orthopaedic *surgery* for a fracture, knee or hip replacement, spinal stenosis, or correction of a bone deformity may be appropriate.[4,7,8] A calcitonin or bisphosphonate may be given for up to 3 months before surgery in order to reduce bone vascularity and minimise blood loss during the operation,[2,4,7] although this effect has not been verified in studies.[8] Such treatment also helps to prevent development of hypercalcaemia due to prolonged immobilisation.[4]

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Renal osteodystrophy

Patients with chronic renal failure (p. 1781.1) may develop complex changes to bone known as renal osteodystrophy[1-6] as part of the wider metabolic derangement known as chronic kidney disease-mineral and bone disorder (CKD-MBD).[7,8] These are often classified according to the state of bone turnover[1,3,5] and bone biopsy is the gold standard for diagnosis and classification.[2-6] Progressive renal failure is associated with hypocalcaemia, hyperphosphataemia, and some decrease in vitamin D metabolism, which increase the production of parathyroid hormone. This leads to secondary hyperparathyroidism (see below) and **high bone turnover** disease.[1,3-5] This manifests as *osteitis fibrosa*,[1,3-5] a condition characterised by increased osteoclastic and osteoblastic activity, woven and irregular osteoid, and bone marrow fibrosis.[2-6] **Low bone turnover** disease includes *osteomalacia* (see p. 1168.1) and *adynamic bone disease*.[1-5] These are characterised by defective mineralisation, decreased bone formation, and an absence of osteoclasts and osteoblasts; osteoid seams are wider or increased in osteomalacia, but normal or decreased in adynamic bone disease.[1-4,9] Osteomalacia, associated with vitamin D deficiency or aluminium toxicity (which has adverse effects on bone, see p. 1820.3), is decreasing in incidence with the removal of aluminium from dialysate solutions and decreasing use of aluminium-containing phosphate binders.[1-3,5,10] The pathogenesis of adynamic bone disease is not fully understood; its increasing incidence is thought to be due to suppression of parathyroid hormone secretion caused by increased exposure to calcium salts, as phosphate binders or in dialysate fluid, and vitamin D analogues.[1-6,9,10] Risk factors for its development include elderly age, diabetes mellitus, and peritoneal dialysis.[1-3,5,9] **Mixed uraemic osteodystrophy** has features of both high bone turnover with hyperparathyroidism, and defective bone mineralisation or osteomalacia.[1-6]

Patients with renal osteodystrophy may develop **osteopenia** or **osteoporosis**.[11]

Treatment is aimed at preventing bone disease by controlling the plasma concentrations of phosphate, calcium, parathyroid hormone, and correcting vitamin D deficiency; it should therefore be begun early in the course of renal impairment.[1,2,4,5]

- ***Hyperphosphataemia*** (p. 1778.3) is initially controlled with a low-phosphate diet but many patients, especially those on dialysis, also need an oral phosphate binder to complex with dietary phosphate in the gastrointestinal tract and reduce its absorption.[1,4]
  Calcium salts such as the carbonate or acetate are effective phosphate binders and have been found to suppress parathyroid hormone concentrations.[1,2,4,12] Calcium citrate is not recommended, because it increases intestinal aluminium absorption.[3,4,12] Calcium salts also raise plasma-calcium concentrations but hypercalcaemia can occur.[4,9] The use of dialysis fluids with a lower calcium content has been suggested for these patients.[4] Use of calcium can also contribute to the development of adynamic bone disease[1,9] and precipitate exogenous calcium deposition in the soft tissues;[1,9,12] coronary artery calcification is a particular problem contributing to cardiac mortality in patients with chronic renal failure.[2-4,13] Hyperphosphataemia or use of vitamin D can exacerbate calcification.[4,12,13]
  Aluminium-based phosphate binders have been given but relatively large doses are required and, as mentioned above, aluminium accumulation can lead to osteomalacia and adynamic bone disease in patients with impaired renal function; their use is no longer generally recommended.[2,3,12] Magnesium carbonate also binds phosphate, but may cause hypermagnesaemia and interfere with bone mineralisation.[2] Dialysate magnesium content may need to be reduced.[4]
  Other phosphate binders that do not contain calcium or aluminium have been tried. Sevelamer is a cationic polymer capable of binding phosphate[2,3] without affecting serum calcium.[4] It has been shown to be equivalent to calcium-based binders,[2,3,12] and is effective in dialysis patients.[1] It has been reported to reduce calcium scores in the coronary artery when compared with calcium salts.[4] Lanthanum carbonate is a cation with a high affinity for phosphate and similar efficacy to calcium carbonate.[3] It has been used effectively in dialysis patients but long-term potential toxic effects are as yet undetermined.[4]
- *Vitamin D* compounds that do not require renal hydroxylation, such as calcitriol or its synthetic analogue, alfacalcidol, are used to correct ***hypocalcaemia*** and to contribute to the control of ***secondary hyperparathyroidism***;[1,4] *calcium supplements* may also occasionally be required. Oversuppression of parathyroid hormone concentration should be avoided to deter the development of adynamic bone disease.[1] Calcitriol is given orally at first, but may also be given intravenously or intraperitoneally to patients on dialysis;[2,4-6] doses are adjusted according to response but the effect should be carefully monitored as hypercalcaemia and hyperphosphataemia may develop.[1,4,5] Use of alfacalcidol in the early stages of renal failure, before dialysis is required, has been reported to improve subclinical bone disease.[1] Newer vitamin D analogues suppress parathyroid activity but with potentially less effect on serum calcium and phosphate;[2-4,13] these include doxercalciferol, maxacalcitol, paricalcitol, and falecalcitriol (see Hyperparathyroidism, p. 2115.2).
  Calcimimetics increase the sensitivity of the calcium-sensing receptor of the parathyroid cells.[3] *Cinacalcet* has reduced parathyroid hormone concentrations[2] without inducing hypercalcaemia or hyperphosphataemia[13] in dialysis patients.

Patients with hyperparathyroidism unresponsive to drug therapy, or who develop hypercalcaemia (which may itself further aggravate the decline in renal function), may require sub-total or total parathyroidectomy.[2-4] There is a risk of inducing a low turnover bone state; hyperparathyroidism can also recur after surgery.[4] Bone mineral density improves after surgery.[2]

Bisphosphonates can be used in the acute management of hypercalcaemia,[2] but seem to be of little use in the long-term treatment of hyperparathyroidism. They may be effective in increasing bone mineral density in haemodialysis patients.[3] Some, however, consider their use is unjustified, even in those with documented osteopenia or osteoporosis, and that they may exacerbate adynamic bone disease due to their effects on bone mineralisation.[11]

- ***Adynamic bone disease*** is treated by stimulating parathyroid hormone-driven bone turnover and mineralisation.[2,3] Calcium and vitamin D supplementation may need to be reduced or stopped, and dialysate calcium concentrations reduced.[2,9] Aluminium deposition needs to be excluded; the use of aluminium-based phosphate binders is clearly undesirable in these patients.[2,9] On bone biopsy, if aluminium accumulation is evident, chelation with *desferrioxamine* may be considered.[2,4]
- ***Osteomalacia*** may respond to vitamin D treatment.[2]
- Treatment of ***mixed uraemic osteodystrophy*** involves management of both hyperparathyroidism and mineralisation defects.[2]

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Rickets

See Osteomalacia and Rickets, p. 1168.1.

Parathyroid Disorders

Parathyroid hormone, secreted by the parathyroid glands, maintains concentrations of ionised calcium in extracellular fluid within normal limits. It acts directly on the kidney to enhance renal reabsorption of calcium, to increase phosphate excretion, and to promote the conversion of vitamin D to its active metabolite, 1,25-dihydroxycholecalciferol, which in turn, enhances calcium absorption from the gastrointestinal tract. Parathyroid hormone also acts on bone, to accelerate bone resorption and the release of calcium and phosphate into the extracellular fluid. Secretion of parathyroid hormone is primarily regulated by the extracellular concentration of ionised calcium; hypocalcaemia stimulates secretion whereas hypercalcaemia has an inhibitory effect. 1,25-Dihydroxycholecalciferol can also suppress parathyroid hormone secretion.

Disorders of parathyroid hormone secretion cause a disruption of calcium homoeostasis and in the long-term, may result in bone disease.

Hyperparathyroidism

Primary hyperparathyroidism is a disorder of parathyroid hormone hypersecretion usually caused by adenomas or hyperplasia of the parathyroid glands; parathyroid carcinoma is a rare cause.[1-4] Patients are often asymptomatic, or have non-specific constitutional symptoms such as fatigue, weakness, anorexia, or bone pain.[3-6] About 20% of patients present with nephrolithiasis, overt bone disease, or neuromuscular weakness.[5] Symptoms and signs of hypercalcaemia (p. 1778.1) may occur;[3,5] hypercalcaemia is usually mild or even intermittent, and severe hypercalcaemia is rare.[7]

Secondary hyperparathyroidism is common in chronic renal failure (p. 1781.1). Other causes of hypocalcaemia or vitamin D deficiency resulting in increased parathyroid hormone secretion include dietary

deficiencies or malabsorption, or lack of exposure to sunlight.[1,3] While patients may also be asymptomatic, manifestations can include arthritis, bone pain, myopathy, tendon rupture, or complications such as coronary artery calcification and calciphylaxis; symptoms of the underlying cause can occur.[3]

Tertiary hyperparathyroidism results from autonomous hypersecretion by the parathyroid gland in patients with long-standing secondary hyperparathyroidism, and often occurs after kidney transplantation.[1,3]

Surgical parathyroidectomy is the **treatment** of choice for symptomatic ***primary hyperparathyroidism***.[1-4,6,8] In patients with asymptomatic primary hyperparathyroidism, no treatment may be necessary, and patients are monitored for serum calcium, serum creatinine, and bone mineral density;[3,5,6,9] the timing of any surgical intervention has been subject to debate.[1,2,4]

In patients for whom surgery is not an option, hypercalcaemia must be controlled. Restriction of dietary calcium is not generally recommended, as this may raise parathyroid hormone levels further.[3,5,6,9,10] While *vitamin D* supplementation may be reasonable in patients with low concentrations of 1,25-dihydroxycholecalciferol, high doses can worsen hypercalcaemia and cause hypercalciuria.[3] Oral *phosphate* supplements have been given in the short-term to alleviate hypercalciuria and hypercalcaemia; intravenous use is no longer recommended.[9] The more potent *bisphosphonates* can be used in the acute management of hypercalcaemia,[9] but seem to be of little benefit in the long-term treatment of hyperparathyroidism.[1,9] However, bisphosphonates such as alendronate may be of use in those patients with low bone mineral density.[3,5,8-12] Although *calcitonins* have a rapid hypocalcaemic effect it is usually short-lived;[9] they are therefore generally given as adjunctive therapy with a bisphosphonate.[2] *Oestrogens* have been reported to increase bone mineral density in postmenopausal women with primary hyperparathyroidism, and to have a small effect on calcium concentrations;[5] however, the high doses needed, and the risks associated with HRT, generally preclude their use.[3,5,6] *Raloxifene*, a selective oestrogen receptor modulator, may be an alternative, having been found to decrease serum calcium and bone turnover in a small, short-term study.[13] Calcium receptor agonists (calcimimetics) may be of benefit in primary hyperparathyroidism by increasing the sensitivity of the calcium-sensing receptor.[5,8-10] In a small dose-finding study,[14] *cinacalcet* decreased serum calcium and lowered parathyroid hormone concentrations without increasing urinary calcium excretion in all dose groups. A larger, placebo-controlled study by the same group found that cinacalcet rapidly normalised serum calcium and modestly decreased parathyroid hormone concentrations; this effect was sustained over 52 weeks.[15] Use of parathyroid hormone peptides to induce autoantibodies against parathyroid hormone resulted in improvement in hypercalcaemia in a woman with parathyroid carcinoma.[16]

Treatment of ***secondary hyperparathyroidism*** is usually aimed at the underlying cause of the hypocalcaemia;[1] early treatment of patients with chronic renal failure can prevent or delay its onset. Treatment is based on appropriate vitamin D replacement and reduction of hyperphosphataemia.[1,3] Oral phosphate binders bind dietary phosphate in the gastrointestinal tract reducing its absorption.[1,3] These have included *calcium salts* such as the carbonate and acetate, which raise serum calcium but carry the risk of inducing hypercalcaemia. *Aluminium hydroxide* also binds phosphate, but can cause osteomalacia (p. 1168.1) and adynamic bone disease (see Renal Osteodystrophy, p. 1170.1). *Sevelamer* is a polymer that does not contain calcium or aluminium, and is capable of binding phosphate.[3] *Vitamin D* compounds that do not require renal hydroxylation for activation, such as calcitriol or its analogue alfacalcidol, are used to lower parathyroid hormone, but the high doses required can induce hypercalcaemia and hyperphosphataemia;[3] newer analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol (see p. 2115.2). *Cinacalcet* is also given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and on haemodialysis. A systematic review[17] of 8 placebo-controlled studies in this patient group concluded that cinacalcet was effective in decreasing concentrations of parathyroid hormone, and serum calcium and phosphorus. However, further studies were needed to ascertain the benefits of calcimimetics over standard therapy and to confirm improvements in patient-based outcomes such as parathyroidectomy rates, fracture, renal osteodystrophy, cardiovascular disease, and mortality.

In patients refractory to medical therapy for secondary hyperparathyroidism, parathyroidectomy may be an option; percutaneous ethanol injection has been used as an alternative.[3,10] Kidney transplantation (p. 1939.2) may cause regression of secondary hyperparathyroidism in some patients, but the condition recurs in about a third of renal graft recipients.[1]

Tertiary hyperparathyroidism is usually treated with surgery.[1,3]

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Hypoparathyroidism

Hypoparathyroidism occurs when there is a deficiency of parathyroid hormone secretion. This may be due to damage or destruction of the glands, e.g. by surgery[1] or disease.[2] Hypoparathyroidism can also arise from auto-immune disease, agenesis of the parathyroid glands (DiGeorge syndrome), defective synthesis of parathyroid hormone (familial hypoparathyroidism), or mutations of the parathyroid and renal calcium-sensing receptors (autosomal dominant hypocalcaemic hypercalciuria) leading to defective regulation of parathyroid hormone secretion.[1,2] Other factors that may lead to a deficiency in parathyroid hormone include hypomagnesaemia and parathyroid adenomas. Where the deficiency results from resistance to parathyroid hormone the condition is termed **pseudohypoparathyroidism**.[1] Parathyroid hormone, as teriparatide, is used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism leads to hypocalcaemia and hyperphosphataemia,[1,3] although in some patients these may not become significant until there is an increased calcium demand, as in pregnancy. Vitamin D deficiency also develops.[1,3] Clinical features reflect the underlying cause of the hypoparathyroidism, but if it occurs rapidly, hypocalcaemia can be acute, with consequent paraesthesia, tetany, and seizures.[1] In chronic hypoparathyroidism, chronic hypocalcaemia may cause cataracts and visual impairment.[1] Hypomagnesaemia and metabolic alkalosis may also occur.[3]

Treatment is aimed at correcting the hypocalcaemia (p. 1778.2) that results mainly from decreased renal tubular calcium resorption.[3] In patients with acute hypocalcaemic tetany parenteral doses of *calcium salts*, along with either oral or parenteral *calcitriol*, may be necessary.[1,3] In those with chronic hypocalcaemia treatment is usually with oral calcium, such as calcium carbonate (which has the advantage of binding phosphate), and vitamin D compounds such as calcitriol (which increase the intestinal absorption of calcium).[1,3] Calcium concentrations and renal function require careful monitoring as resultant hypercalcaemia can cause hypercalciuria, nephrolithiasis, and renal damage.[1] *Thiazide diuretics* may also minimise renal calcium losses.[3] Efficacy of treatment may vary depending on the underlying cause.[1,2]

Teriparatide has been shown to be effective in the treatment of chronic hypoparathyroidism. In 2 studies comparing it with calcium and calcitriol treatment,[4,5] teriparatide maintained serum calcium in the normal range, and decreased urine calcium excretion.

Parathyroid tissue *transplantation* is rarely possible as allografts require immunosuppression. Autografting may result in recurrence of pre-parathyroidectomy hyperparathyroidism.[1] However, good results have been reported after transplantation of parathyroid cells, depleted of antigen-bearing cells, in a few patients with postsurgical hypoparathyroidism.[6,7]

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Alendronate

ATC — M05BA04.
ATC Vet — QM05BA04.
UNII — X1J18R4W8P.

Alendronic Acid *(BAN, rINN)*

Acide Alendronique; Ácido alendrónico; Acidum Alendronicum; AHButBP; Alendrónico, ácido; Alendronihappo; Alendronik Asit; Alendronsyra; Aminohydroxybutylidene Diphosphonic Acid; Алендроновая Кислота.

4-Amino-1-hydroxybutane-1,1-diylbis(phosphonic acid).

$C_4H_{13}NO_7P_2$=249.1

CAS — 66376-36-1.
ATC — M05BA04.
ATC Vet — QM05BA04.

Alendronate Sodium *(USAN, rINNM)*

Alendronat Sodyum; Alendronate de Sodium; Alendronato sódico; G-704650; L-670452; MK-0217; MK-217; Monosodium alendronate; Natrii Alendronas; Natrii Alendronas Trihydricus; Natrio alendronatas; Natriumalendronaatti; Natriumalendronat; Nátrium-alendronát; Natrium-alendronát trihydrát; Sodium Alendronate (BANM); Sodium, alendronate de; Натрий Алендронат.

Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate trihydrate.

$C_4H_{12}NNaO_7P_2.3H_2O$=325.1

CAS — 121268-17-5.
ATC — M05BA04.
ATC Vet — QM05BA04.
UNII — 2UY4M2U3RA (alendronate sodium trihydrate); 4988K7X26P (anhydrous alendronate sodium).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sodium Alendronate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dichloromethane; very slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0.

USP 36: (Alendronate Sodium). A white, free-flowing powder. Soluble in water; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in isopropyl alcohol; very slightly soluble in dimethyl sulfoxide, in methyl alcohol, and in propylene glycol.

Uses and Administration

Alendronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It is a potent inhibitor of bone resorption and is given in the management of osteoporosis either alone or with vitamin D. Alendronate is used for the treatment of Paget's disease of bone. It has also been given in the treatment of bone metastases and hypercalcaemia of malignancy.

Alendronate is given orally as the sodium salt, but doses are expressed in terms of alendronic acid; alendronate sodium 1.3 mg is equivalent to about 1 mg of alendronic acid. The specific instructions given in Adverse Effects and Precautions, p. 1172.3 should be followed to minimise adverse effects and permit adequate absorption.

The usual dosage for the treatment of **osteoporosis** in men and postmenopausal women is 10 mg daily. Postmenopausal women may be given 5 mg daily for prophylaxis. It may also be given once weekly to postmenopausal women in a dose of 70 mg for treatment of osteoporosis, or 35 mg for prophylaxis. Men with osteoporosis may be treated with 70 mg once weekly.

For the treatment of corticosteroid-induced osteoporosis a dose of 5 mg daily is given; postmenopausal women who do not take HRT should be given 10 mg daily for treatment or prevention.

In adults with **Paget's disease** of bone the usual dose is 40 mg daily for 6 months; treatment may be repeated if necessary after an interval of a further 6 months.

For details of administration in renal impairment, see below.

Alendronate has also been given by intravenous infusion.

Administration. Alendronate once-weekly was considered to be therapeutically equivalent to once-daily dosing in both the treatment[1,2] and prevention[3] of osteoporosis, although the treatment study[1] was considered[4,5] to lack information about other drugs being taken and reasons for withdrawal, and studied bone mineral density, not fracture. Tolerability of a once-weekly regimen was comparable to placebo in one study[6] and to once-daily dosing in another;[7] a review[5] concluded that weekly dosage carried a lower risk of upper gastrointestinal symptoms.

1. Schnitzer T, *et al.* Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)* 2000; 12: 1–12.
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Administration in renal impairment. Elimination of alendronate is reduced in *rats* with kidney failure and is likely to be reduced in patients with renal impairment. Licensed product information makes the following recommendations for oral dosage based on creatinine clearance (CC):

- mild to moderate renal impairment (CC greater than 35 mL/minute): no dose adjustment needed
- severe renal impairment (CC less than 35 mL/minute): use is not recommended due to lack of experience with alendronate in this population

Charcot neuroarthropathy. Bisphosphonates, including alendronate, have been tried for Charcot neuroarthropathy, see under Bisphosphonates, p. 1174.1.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous alendronate 7.5 mg daily for 3 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Adami S, *et al.* Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; 56: 201–4.

Gaucher disease. In a placebo-controlled study of patients with Gaucher disease (p. 2433.3), the addition of oral alendronate 40 mg daily to enzyme therapy increased lumbar bone mineral density, but had no effect on focal lesions;[1] the authors concluded that alendronate may be useful adjunctive therapy especially in those patients at risk of osteopenic fracture.

1. Wenstrup RJ, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004; 104: 1253–7.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. A randomised dose-response study[1] found that single intravenous doses of alendronate 5 mg or more effectively lowered serum-calcium concentrations in patients with tumour-induced hypercalcaemia. Alendronate has also been used to treat hypercalcaemia associated with vitamin D intoxication in children.[2,3]

1. Nussbaum SR, *et al.* Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. *J Clin Oncol* 1993; 11: 1618–23.
2. Orbak Z, *et al.* Vitamin D intoxication and therapy with alendronate (case report and review of literature). *Eur J Pediatr* 2006; 165: 583–4.
3. Doneray H, *et al.* Intragastric alendronate therapy in two infants with vitamin D intoxication: a new method. *Clin Toxicol* 2008; 46: 300–2.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p. 1170.3), but seem to be of little benefit for long-term treatment. In patients with primary hyperparathyroidism, oral alendronate significantly increased bone mineral density, especially at the lumbar spine; virtually all of this gain appeared to occur within the first year of treatment. Alendronate is considered to be useful in those patients for whom parathyroidectomy is not possible.[1-4]

1. Rossini M, *et al.* Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. *J Bone Miner Res* 2001; 16: 113–19.
2. Parker CR, *et al.* Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. *J Clin Endocrinol Metab* 2002; 87: 4482–9.
3. Chow CC, *et al.* Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; 88: 581–7.
4. Khan AA, *et al.* Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; 89: 3319–25.

Malignant neoplasms of the bone. For information on the use of bisphosphonates for metastatic bone disease, see Malignant Neoplasms of the Bone, under Bisphosphonates, p. 1174.1.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including alendronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Alendronate significantly increases bone mineral density (BMD) of the lumbar spine and femoral neck in **postmenopausal women** with osteoporosis;[1,2] it increases vertebral BMD in postmenopausal women without osteoporosis, but not quite to the same extent as HRT.[1]

Continuous long-term therapy appears to be more effective than short-term treatment in terms of skeletal benefits,[1-4] but a residual effect on BMD remains for several years after stopping treatment,[3-5] despite resumption of bone loss after withdrawal of alendronate.[4-6] Studies[7,8] in early postmenopausal women suggested that a *higher initial dosage* might be more effective in terms of BMD gain and residual effect.

The effect of alendronate on fracture risk may depend on *baseline bone mineral density*.[2] Treatment reduced the incidence of new vertebral and nonvertebral fractures in women with prior fractures; in women without prior fractures, alendronate reduced the incidence of clinical fractures in those with osteoporosis,[9] but not in those with higher BMD.[10] A systematic review[11] found that alendronate showed a clinically important benefit in the secondary prevention of all osteoporotic fractures; statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were seen. No significant reductions were found for primary prevention of osteoporotic fractures, but the reduction in vertebral fractures with alendronate was deemed to be clinically important.

Alendronate is also used in **men** with osteoporosis; in a 2-year randomised study, an oral dose of 10 mg daily increased vertebral and nonvertebral BMD and helped prevent vertebral fractures.[12] Oral alendronate 70 mg weekly also increased BMD significantly in osteoporotic men after 1 year when compared to placebo; fracture incidence, not a primary end-point, was similar in both groups.[13]

Alendronate also increases bone mass density in men and women receiving oral **corticosteroids** at doses equivalent to at least 7.5 mg prednisone daily,[14,15] and may be of some benefit in reducing bone loss after heart[16] and liver[17] **transplantation.**

In men with prostate cancer given androgen deprivation therapy, BMD of the spine and hip significantly improved in those given once-weekly alendronate for 1 year compared with those given calcium and vitamin D supplementation alone.[18] A second year of once-weekly alendronate gave continued improvements in BMD, whereas stopping resulted in bone loss and increased bone turnover. A 1-year delay in starting bisphosphonate treatment resulted in smaller gains in BMD compared with those who were given early treatment.[19]

Limited available data suggest that alendronate may be safe and effective for patients with HIV who have decreased BMD.[20]

1. Sharpe M, *et al.* Alendronate: an update of its use in osteoporosis. *Drugs* 2001; 61: 999–1039.
2. Pérez-López FR. Postmenopausal osteoporosis and alendronate. *Maturitas* 2004; 48: 179–92.
3. Tonino RP, *et al.* Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000; 85: 3109–15.
4. Bone HG, *et al.* Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; 350: 1189–99.
5. Black DM, *et al.* PLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; 296: 2927–38.
6. Ravn P, *et al.* Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. *J Clin Endocrinol Metab* 2000; 85: 1492–7.
7. Sambrook PN, *et al.* Alendronate in the prevention of osteoporosis: 7-year follow-up. *Osteoporosis Int* 2004; 15: 483–8.
8. McClung MR, *et al.* Early Postmenopausal Intervention Cohort (EPIC) Group Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab* 2004; 89: 4879–85.
9. Black DM, *et al.* Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. *J Clin Endocrinol Metab* 2000; 85: 4118–24.
10. Cummings SR, *et al.* Effect of alendronate on risk of fracture in wome with low bone density but without vertebral fractures: results from th Fracture Intervention Trial. *JAMA* 1998; 280: 2077–82.
11. Wells GA, *et al.* Alendronate for the primary and secondary preventio of osteoporotic fractures in postmenopausal women. Available in Th Cochrane Database of Systematic Reviews; Issue 1. Chichester: Joh Wiley; 2008 (accessed 15/04/08).
12. Orwoll E, *et al.* Alendronate for the treatment of osteoporosis in men. *Engl J Med* 2000; 343: 604–10.
13. Miller PD, *et al.* Weekly oral alendronic acid in male osteoporosis. *Cl Drug Invest* 2004; 24: 333–41.
14. Saag KG, *et al.* Alendronate for the prevention and treatment c glucocorticoid-induced osteoporosis. *N Engl J Med* 1998; 339: 292–9.
15. de Nijs RNJ, *et al.* STOP Investigators. Alendronate or alfacalcidol t glucocorticoid-induced osteoporosis. *N Engl J Med* 2006; 355: 675–84.
16. Shane E, *et al.* Alendronate versus calcitriol for the prevention of bon loss after cardiac transplantation. *N Engl J Med* 2004; 350: 767–76.
17. Atamaz F, *et al.* The prevention of bone fractures after live transplantation: experience with alendronate treatment. *Transplan Proc* 2006; 38: 1448–52.
18. Greenspan SL, *et al.* Effect of once-weekly oral alendronate on bone los in men receiving androgen deprivation therapy for prostate cancer: randomized trial. *Ann Intern Med* 2007; 146: 416–24.
19. Greenspan SL, *et al.* Skeletal health after continuation, withdrawal, o delay of alendronate in men with prostate cancer undergoing androgen deprivation therapy. *J Clin Oncol* 2008; 26: 4426–34.
20. Lin D, Rieder MJ. Interventions for the treatment of decreased bon mineral density associated with HIV infection. Available in Th Cochrane Database of Systematic Reviews; Issue 2. Chichester: Joh Wiley; 2007 (accessed 15/04/08).

Paget's disease of bone. Bisphosphonates may be indi cated for patients with Paget's disease of bone (p. 1169.3 if bone pain is persistent, or to prevent further progressior of the disease. Oral alendronate 40 mg daily for 6 month was more effective than etidronate or placebo in the treat ment of Paget's disease,[1] although an earlier study[2] founc a more sustained reduction in biochemical markers wit an oral dose of 80 mg daily. Alendronate has also beer shown to be as effective as pamidronate in previously untreated patients, but in those who had previously been treated with pamidronate alendronate was markedly more effective in producing biochemical remission.[3]

1. Reid IR, Siris E. Alendronate in the treatment of Paget's disease of bone *Int J Clin Pract* 1999; 101 (suppl): 62–6.
2. Khan SA, *et al.* Alendronate in the treatment of Paget's disease of bone. *Bone* 1997; 20: 263–71.
3. Walsh JP, *et al.* A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. *Bone* 2004; 34: 747–54.

Polymyositis and dermatomyositis. Alendronate has been reported to be effective in the treatment of calcinosis associated with juvenile dermatomyositis (p. 1611.1).

1. Mukamel M, *et al.* New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment. *J Pediatr* 2001; 138: 763–6.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Gastrointestinal symptoms such as abdominal pain, dyspepsia, diarrhoea or constipation are the most frequent adverse effects with alendronate. Severe oesophageal reactions such as oesophagitis, erosions, ulceration, and stricture have occurred (see p. 1173.1); patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as dysphagia, new or worsening heartburn, pain on swallowing, or retrosternal pain. Peptic ulceration has also been reported.

Alendronate should not be given to patients with abnormalities of the oesophagus or other factors that might delay oesophageal emptying, or those unable to stand or sit upright for at least 30 minutes. It should be used with caution in patients with upper gastrointestinal abnormalities. To minimise the risk of oesophageal reactions:

- patients should be instructed to swallow alendronate tablets whole with plenty of water (not less than 200 mL), in an upright position (standing or sitting). Mineral water with a high concentration of calcium should be avoided
- tablets should be taken on rising for the day, on an empty stomach, at least 30 minutes before breakfast and any other oral medication
- patients should remain upright for at least 30 minutes after taking the tablets, and should not lie down before eating the first meal of the day
- alendronate should not be taken at bedtime, or before getting up for the day

Hypocalcaemia should be corrected before starting alendronate therapy, and other disorders affecting mineral metabolism such as vitamin D deficiency or hypoparathyroidism should also be treated; serum calcium in these patients should be monitored during therapy.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, including alendronate, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including alendronate, see under Bisphosphonates, p. 1175.2.

Effects on the heart. For discussion of a possible increased risk of serious atrial fibrillation with bisphosphonates, including alendronate, see Effects on the Heart, under Bisphosphonates, p. 1175.3.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including alendronate, see under Bisphosphonates, p. 1176.1.

Effects on the liver. Hepatitis[1,2] and hepatocellular damage with raised liver enzyme concentrations[3,4] have been reported after therapy with alendronate.

1. Lieverse RJ. Hepatitis after alendronate. *Neth J Med* 1998; 53: 271–2.
2. Carrère C, *et al.* Hépatite aiguë sévère imputable á l'alendronate. *Gastroenterol Clin Biol* 2002; 26: 179–80.
3. Halabe A, *et al.* Liver damage due to alendronate. *N Engl J Med* 2000; 343: 365.
4. de la Serna Higuera C, *et al.* Lesión hepatocelular inducida por alendronato. *Gastroenterol Hepatol* 2001; 24: 244–6.

Effects on mental state. Auditory hallucinations and red-coloured visual disturbances were reported[1] in a patient taking alendronate for osteoporosis.

1. Coleman CI, *et al.* Alendronate-induced auditory hallucinations and visual disturbances. *Pharmacotherapy* 2004; 24: 799–802.

Effects on the musculoskeletal system. A 63-year old woman given alendronate 70 mg once weekly for osteoporosis developed diffuse severe myalgia and transient acute symmetrical polyarthritis 12 hours after ingestion. Symptoms did not recur after stopping the drug.[1] From the initial marketing of alendronate up until November 2002, the FDA had received reports of severe bone, joint, and/or muscle pain in 118 patients, including a child given the drug in error. Of 83 patients for whom information was available, 55 improved after stopping alendronate; in most of these improvement was gradual, although some experienced immediate relief. Nine of these 83 patients had recurrence of pain when given alendronate again. It was suggested that pain might tend to be underreported since it is subjective, and might be attributed to underlying osteoporosis.[2] As of May 2006, 7 cases of synovitis linked to alendronate use had been reported in New Zealand; in one case, severe synovitis caused carpal tunnel syndrome that required urgent decompression.[3]

Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

1. Gerster JC, Nicole F. Acute polyarthritis related to once-weekly alendronate in a woman with osteoporosis. *J Rheumatol* 2004; 31: 829–30.
2. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; 165: 346–7.
3. Savage R. Alendronate and inflammatory adverse reactions (Issued May 2006). Available at: http://www.medsafe.govt.nz/profs/puarticles/alendinflam.htm#Myalgia (accessed 15/04/08)

Effects on the oesophagus. Between September 1995 and March 1996 the UK CSM had received 10 reports of adverse effects on the oesophagus in patients receiving alendronate sodium.[1] Of these, 4 were of oesophageal reflux, 4 of oesophagitis, and 2 of oesophageal ulceration. As of March 1996, worldwide an estimated 475 000 patients had received alendronate and 199 patients had oesophageal reactions reported to the manufacturer, of which 51 were serious or severe.[2] Endoscopic findings included erosions, ulcerations, exudative inflammation, and thickening of the oesophagus. Bleeding was rare, and oesophageal perforation was not reported. Most oesophageal reactions occurred within 1 week to 2 months of starting alendronate therapy. Recovery occurred when alendronate was stopped; however, it was considered important that patients be followed up for the possible development of strictures.[2] In about 60% of the cases where the information was available, alendronate had not been taken in accordance with the precautions for use (see p. 1172.3).

The CSM subsequently noted[3] that it had continued to receive reports of reactions; by July 1998 there had been 97 reports in the UK, in 1 case associated with a fatality. It was estimated that 1 to 2% of patients might experience oesophageal reactions even when following the precautions for use. Some have reported a much higher incidence of unacceptable upper gastrointestinal symptoms in clinical practice.[4] However, a large placebo-controlled trial of alendronate did not find any increase in upper gastrointestinal events in patients taking alendronate.[5]

1. CSM/MCA. Oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1996; 22: 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. de Groen PC, *et al.* Esophagitis associated with the use of alendronate. *N Engl J Med* 1996; 335: 1016–21.
3. CSM/MCA. Reminder: severe oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1998; 24: 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)
4. Kelly R, Taggart H. Incidence of gastrointestinal side effects due to alendronate is high in clinical practice. *BMJ* 1997; 315: 1235.
5. Bauer DC, *et al.* Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med* 2000; 160: 517–25.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare, see p. 1177.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alendronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Like other bisphosphonates, alendronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is about 0.4% when taken half an hour before food, reduced from 0.7% in the fasting state; absorption is negligible when taken up to 2 hours after a meal. Plasma protein binding is about 78%. Bisphosphonates do not appear to be metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

References.

1. Gertz BJ, *et al.* Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther* 1995; 58: 288–98.
2. Cocquyt V, *et al.* Pharmacokinetics of intravenous alendronate. *J Clin Pharmacol* 1999; 39: 385–93.
3. Porras AG, *et al.* Pharmacokinetics of alendronate. *Clin Pharmacokinet* 1999; 36: 315–28.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actimax; Alenato; Arendal; Berlex; Brek; Carmotin†; Dronat; Filxine; Findeclin Combi; Findeclin; Fosamax; Lendronal; Marvil; Oseotenk; Osteobon; Osteofene; Osteonate; Pamoseo; Regenesis; Reyoint†; Rixofem; Silidral; Tilios; ***Austral.***: Adronat; Alendro; Alendrobell; Fosamax; Ossmax; ***Austria***: Alendronstad; Fosamax; ***Belg.***: Beenos; Fosamax; ***Braz.***: Alendil; Alendosseo; Bonalen; Cleveron; Endronax; Endrostan; Fosamax; Minusorb; Ostenan; Osteofar; Osteoform; Osteoral; Terost; ***Canad.***: Fosamax; ***Chile***: Aldrox; Arendal; Fosamax Plus; Fosamax; Fosval; Holadren; Leodrin; Osdren; Oseotal; Oseum; Osteosan†; Pasodron; ***China***: Anlun (安仑); Fosamax (福善美); Gubang (固邦); Tian Ke (天可); ***Cz.***: Aldrion†; Alendrogen; Alenwin; Bonalen†; Fosamax; Fosteofos; Gendron; Lindron†; Ralenost†; Siranin; ***Denm.***: Bonasol; Fosamax; ***Fin.***: Bonasol; Fosamax; ***Fr.***: Fosamax; ***Ger.***: Alendro-Q†; Alendromed; Alendron; Fosamax; Tevabone; Tevanate†; ***Gr.***: Aldromax; Aledrolet; Alefos; Alendo; Alendral; Ampine; Arthroplus; Aurodren; Bestalen; Bonedron; Caltera; Dargol; Debenal; Delfoza; Deparex; Difonate; Discozal; Drofaz; Dronalent; Eldinir; En-Por; Enimon; Farmemax; Forosa; Fosalen; Fosamax; Fosandron; Fosazom; Jamax-S; Ledronin; Lozostun; Meldoz; Moralen; Mosmass; Osaston; Ostalert; Ostaven; Osteonat; Osteos; Ostomax; Porocalm; Promax†; Ridon; Riledron; Tevanate; Tivarun; Zakondronate†; Zemaros; Zulgar; ***Hong Kong***: Allentop; Fosamax; Osteofos; ***Hung.***: Alendis; Alendromax; Alendron; Epolar; Fortimax; Fosamax; Massidron; Sedron; Trabecan; ***India***: Alenost; Bifosa; Denfos; Dronal; Osteofos; ***Indon.***: Alexonal†; Alovell; Fosamax†; Nichospor; Osteofar; Voroste; ***Irl.***: Alendromax; Bonasol; Fosalen; Fosamax; Fostepor; Fostolin; Osteomel; Romax; Steovess; Tevanate; ***Israel***: Alendrovenir; Fosalan; Maxibone; Tevanate; ***Ital.***: Adronat; Alendros; Alenic; Bonasol; Doryx; Dronal; Fosamax; Genalen; Glamor; Loss; Nofratil; Porodron; Realen; Tevabone; ***Jpn***: Bonalon; Teiroc; ***Malaysia***: Fosamax; ***Mex.***: Alxis; Apodrolen; Blindafe; Dronadil; Drovitan; Fosamax; Fosfacid†; Landrolen†; Lenadrin; Leodrin; Nafadren; Osso; Sinfract; Synostep; Tonadron†; Zondra; ***Neth.***: Alendratol†; Alendris†; Alendronax; Alendronorm†; Bonasol; Dronatex†; Dronatifer†; Fosamax; Ostadil; Ostaham†; Osteonorm; Randronate; Steovess; ***Norw.***: Fosamax; ***NZ***: Fosamax; ***Philipp.***: Forosa; Fosamax; Tevanate; ***Pol.***: Alenato; Alendran; Alendrogen; AlendroLEK†; Densidron; Fosamax; Lindron†; Osalen†; Ostemax; Ostenil; Ostodronic; Ostolek; Rekostin; Sedron; ***Port.***: Adronat; Alehelm; Aleostito; Bifosal; Blocan; Caldronate; Flamisul; Fosamax; Lendral†; Nozat; ***Rus.***: Forosa (Фороза); Fosamax (Фосамакс); Lindron (Линдрон); Ostalon (Остелон); Osterepar (Остерепар); Strongos (Стронгос); Tevanate (Теванат); ***S.Afr.***: Aldren; Boniran; Fosagen; Fosamax; Ostena; Osteobon; Osteonate; ***Singapore***: Fosamax; ***Spain***: Adelan; Alendrocare; Alendrofarm; Alendrogyn†; Alenvir; Bifoal Semanal; Calbion; Fosamax; Lefosan; Semandrol; ***Swed.***: Alenat; Fosamax; ***Switz.***: Alendron; Fosamax; ***Thai.***: Aldren; Bonmax; Fosamax; Ralenost; ***Turk.***: Alemaks; Andante; Bonacton; Bonemax; Fosamax; Osalen; Osteomax; Vegabon; ***UK***: Fosamax; ***Ukr.***: Alendros (Алендрос)†; Ostalon (Остелон); Ostemax (Остемакс); Osteofos (Остеофос); Ralenost (Раленост)†; ***USA***: Fosamax; ***Venez.***: Aldronac; Aliot; Defixal; Fixopan; Fosamax; Osteodur; OsteoMax; Porosal.

Multi-ingredient Preparations. ***Arg.***: Fosamax Plus; Marvil D; Regenesis Max; Silidral Plus; ***Austral.***: Adronat Plus D-Cal; Adronat Plus; Dronalen Plus D-Cal; Dronalen Plus; Fosamax Plus; ***Austria***: Fosavance; ***Belg.***: Fosavance; ***Braz.***: Alendil Calcio D; Fosamax D; ***Canad.***: Fosavance; ***Chile***: Aldrox-D; Arendal D3; Leodrin Plus; ***China***: Fosamax Plus (福美加); Cz.: Adrovance; Fosavance; Vantavo; ***Denm.***: Fosavance; ***Fin.***: Fosavance; ***Fr.***: Adrovance; Fosavance; ***Ger.***: Fosavance; ***Gr.***: Adrovance; Fosavance; ***Hong Kong***: Fosamax Plus; ***Hung.***: Calcisedron-D; Epolar Trio; Fosavance; ***Indon.***: Fosamax Plus; ***Irl.***: Adrovance; Fosavance; Vantavo; ***Israel***: Fosavance; ***Ital.***: Adrovance; Fosavance; ***Malaysia***: Fosamax Plus; ***Mex.***: Fosamax Plus; ***Neth.***: Adrovance; Alenca D3; Alendromed; Bonendro; Fosavance; Vantavo; ***Norw.***: Fosavance; ***NZ***: Fosamax Plus; ***Philipp.***: Fosavance; ***Pol.***: Adrovance; ***Port.***: Adrovance; Fosavance; Vantavo; ***Rus.***: Fosavance (Фосаванс); Ostalon Calcium-D (Остелон Кальций-Д); Tevabone (Тевабон); ***S.Afr.***: Fosavance; ***Singapore***: Fosamax Plus; ***Spain***: Adrovance; Fosavance; ***Swed.***: Fosavance; ***Switz.***: Fosavance; ***Thai.***: Fosamax Plus; Maxmarvil; ***Turk.***: Fosavance; Vegabon Plus D; ***UK***: Fosavance; ***Ukr.***: Ostalon Calcium-D (Остелон Кальций-Д); ***USA***: Fosamax Plus.

Pharmacopoeial Preparations
BP 2014: Alendronic Acid Tablets;
USP 36: Alendronate Sodium Tablets.

Arzoxifene *(rINN)* ⊗

Arzoxifène; Arzoxifeno; Arzoxifenum; LY-353381; Арзоксифен.

2-(*p*-Methoxyphenyl)-3-[*p*-(2-piperidinoethoxy)phenoxy] benzo[*b*]thiophene-6-ol.

$C_{28}H_{29}NO_4S$=475.6

CAS — 182133-25-1.

UNII — E569WG6E60.

Arzoxifene Hydrochloride *(USAN, rINNM)* ⊗

Arzoxifène, Chlorhydrate d'; Arzoxifeni Hydrochloridum; Hidrocloruro de arzoxifeno; SERM-3; Арзоксифена гидрохлорид.

2-(*p*-Methoxyphenyl)-3-[*p*-(2-piperidinoethoxy)phenoxy] benzo[*b*]thiophene-6-ol hydrochloride.

$C_{28}H_{29}NO_4S,HCl$=512.1

CAS — 182133-27-3.

UNII — FU88PI0433.

Profile

Arzoxifene, like raloxifene (p. 2303.1), is a selective oestrogen receptor modulator; it has been investigated for the prevention and treatment of postmenopausal osteoporosis and to reduce the risk of breast cancer, but results in osteoporosis were disappointing.

References.

1. Deshmane V, *et al.* Phase III double-blind trial of arzoxifene compared with tamoxifen for locally advanced or metastatic breast cancer. *J Clin Oncol* 2007; 25: 4967–73.

Bisphosphonates

Bifosfonáten; Bifosfonati; Bifosfonatos; Biphosphonates; Bisfosfonater; Bisfosfoniany; Difosfonaten; Difosfonati; Difosfonatos; Diphosphonates; Бифосфонаты.

Bisphosphonates are analogues of pyrophosphate, in which the central oxygen atom is replaced by a carbon atom with two further substituents—see Figure 1, p. 1175. Like pyrophosphate they have a strong affinity for bone. The bisphosphonates are used chiefly for their antiresorptive and hypocalcaemic properties (see Uses and Administration, below).

Uses and Administration

The bisphosphonates inhibit bone resorption and thus have a hypocalcaemic effect. They are pyrophosphate analogues that have a high affinity for the hydroxyapatite of bone, and that inhibit bone resorption by osteoclasts; because of the coupling of resorption and formation this results in an overall reduction in remodelling and bone turnover (see Bone and Bone Disease, p. 1167.1). Their antiresorptive potency varies widely. The bisphosphonates also inhibit the formation and dissolution of hydroxyapatite crystals and thus have the potential to interfere with bone mineralisation. The degree to which the bisphosphonates inhibit mineralisation in clinical practice varies; etidronate is the most potent inhibitor of those now in general clinical use.

Because bone resorption increases plasma-calcium concentrations, the bisphosphonates are used as adjuncts to the treatment of severe hypercalcaemia, especially when associated with malignancy. They are also used in disorders associated with excessive bone resorption and turnover, such as Paget's disease of bone and osteoporosis, as well as in the management of bone metastases. Etidronate has been used in the prevention and treatment of ectopic ossification.

The affinity of bisphosphonates for bone allows complexes labelled with radioactive technetium-99m (see p. 2228.1) to be used diagnostically as bone scanning agents.

Bisphosphonates have been given by intravenous infusion or orally. In the latter case food should be avoided for a suitable period before and after a dose, especially foods with a high calcium content such as milk.

References.

1. Brown DL, Robbins R. Developments in the therapeutic applications of bisphosphonates. *J Clin Pharmacol* 1999; 39: 651–60.
2. Shoemaker LR. Expanding role of bisphosphonate therapy in children. *J Pediatr* 1999; 134: 264–7.
3. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* 2003; 9: 2643–58.
4. Cohen SB. An update on bisphosphonates. *Curr Rheumatol Rep* 2004; 6: 59–65.
5. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005; 39: 668–77.
6. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics* 2007; 119 (suppl 2): S150–S162.
7. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. *J Dent Res* 2007; 86: 1022–33.
8. Russell RG, *et al.* Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci* 2007; 1117: 209–57.
9. Drake MT, *et al.* Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; 83: 1032–45.

Charcot neuroarthropathy. Six months of treatment with once-weekly alendronate has been reported[1] to improve signs and symptoms of Charcot neuroarthropathy (a sometimes painful deformity in limbs that have lost sensory innervation). Zoledronic acid has also been tried, but was not found to be effective.[2]

1. Pitocco D, *et al.* Six-month treatment with alendronate in acute Charcot neuroarthropathy: a randomized controlled trial. *Diabetes Care* 2005; 28: 1214–15.
2. Pakarinen T-K, *et al.* The effect of zoledronic acid on the clinical resolution of Charcot neuroarthropathy: a pilot randomized controlled trial. *Diabetes Care* 2011; 34: 1514–16.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients.

Ectopic ossification. Bisphosphonates that are potent inhibitors of mineralisation such as etidronate have been advocated for prevention of ectopic ossification (p. 103.2), but they do not prevent the formation of the osteoid matrix, and delayed mineralisation may occur once they are withdrawn.

Hypercalcaemia. In patients with severe symptomatic hypercalcaemia restoration and maintenance of adequate hydration and urine flow is essential, and helps to reduce plasma-calcium concentrations by promoting calcium diuresis. In hypercalcaemia of malignancy (p. 1167.2) therapy with inhibitors of bone resorption such as the bisphosphonates is used. Although sustained, the action of bisphosphonates is not particularly rapid; they may be used with a calcitonin where both rapid and prolonged diminution of plasma-calcium concentration is desired.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p. 1170.3), but seem to be of little benefit for long-term treatment.

Juvenile idiopathic arthritis. Bisphosphonates may have a role[1] in preventing low bone mineral density and fragility fractures in children with juvenile idiopathic arthritis (p. 12.1).

1. Thornton J, *et al.* Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child* 2006; 91: 753–61.

Malignant neoplasms of the bone. There is good evidence that some bisphosphonates are of benefit in treatment of patients with metastatic bone disease (see p. 700.3).

Due to the high cumulative doses of bisphosphonates used in cancer patients, there is a higher risk of osteonecrosis of the jaw, see p. 1176.3. Treatment strategies have been suggested to limit the risk of adverse effects while maintaining efficacy. In multiple myeloma (see p. 699.2), some have recommended[1,2] that monthly intravenous bisphosphonate therapy continue for 2 years. After 2 years, therapy can be stopped in those who have achieved a complete response or who are in a stable plateau phase. If disease is still active, frequency of infusion can be decreased to once every 3 months. However, others recommend stopping therapy after 1 year in those with a complete response or very good partial response. For those with a poorer response and ongoing active bone disease, bisphosphonates may be continued for up to 2 years.[3] In newly diagnosed patients, pamidronate is favoured over zoledronate as data suggest the risk of osteonecrosis may be higher with the latter.[1-3] However, routinely switching patients from zoledronate to pamidronate is not recommended, as no data suggest that this will prevent osteonecrosis. Multiple myeloma patients without evidence of skeletal involvement should not routinely be given bisphosphonates.[3]

There is also much interest in the use of bisphosphonates to **prevent** the development of bone metastases; however, preliminary evidence of their efficacy is conflicting. Specific references for the management of bone metastases may be found under the individual drugs.

1. Lacy MQ, *et al.* Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. *Mayo Clin Proc* 2006; 81: 1047–53.
2. Kyle RA, *et al.* American Society of Clinical Oncology. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; 25: 2464–72. Also available at: http://jco.ascopubs.org/cgi/reprint/JCO.2007.12.1269v1.pdf (accessed 12/02/09)
3. Durie BGM, *et al.* International Myeloma Working Group. Use of bisphosphonates in multiple myeloma: IMWG response to Mayo Clinic consensus statement. *Mayo Clin Proc* 2007; 82: 516–7; author reply 517–18.

Malignant neoplasms of the breast. Preliminary data suggested that zoledronate might have antitumour effects that could reduce the risk of breast cancer progression.[1] An analysis[2] of interim results from 2 studies in postmenopausal women treated with letrozole for early breast cancer reported that patients who were also treated with zoledronate from the start had a lower 12-month rate of breast cancer recurrence compared with those who had treatment delayed until bone loss became clinically significant or a fragility fracture occurred. A subsequent study[3] in premenopausal women with oestrogen receptor-positive early breast cancer found that addition of zoledronate to adjuvant endocrine therapy improved disease-free survival at about 4 years, compared with endocrine therapy alone. Epidemiological data have suggested that this may be a class effect. Treatment with oral bisphosphonates for longer than 1 year was found to be associated with a reduced risk of postmenopausal breast cancer in one case-control study.[4] Additionally, a cohort study[5] found a lower incidence of invasive breast cancer in postmenopausal women treated with the oral bisphosphonates alendronate, etidronate, pamidronate, and tiludronate. Fewer oestrogen-positive breast cancers were diagnosed in the bisphosphonate group, and there was a trend towards fewer oestrogen-negative breast cancers; however, the incidence of ductal carcinoma *in situ* was increased, and the authors suggested that bisphosphonates may prevent *in-situ* carcinomas from progressing to invasive cancer. The AZURE study, where 5 years of intravenous zoledronic acid was added to standard chemotherapy or hormonal therapy for premenopausal or postmenopausal women with breast cancer, reported no improvement in overall survival or recurrence with zoledronic acid treatment, although a subgroup of 1100 women who were at least 60 years of age or postmenopausal for more than 5 years had a 29% reduced risk of dying from breast cancer.[6]

1. Lyseng-Williamson KA. Zoledronic acid: a review of its use in breast cancer. *Drugs* 2008; 68: 2661–82.
2. Brufsky A, *et al.* Z-FAST and ZO-FAST Study Groups. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008; 13: 503–14.
3. Gnant M, *et al.* ABCSG-12 Trial Investigators. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; 360: 679–91.
4. Rennert G, *et al.* Use of bisphosphonates and risk of postmenopausal breast cancer. *J Clin Oncol* 2010; 28: 3577–81.
5. Chlebowski RT, *et al.* Oral bisphosphonate use and breast cancer incidence in postmenopausal women. *J Clin Oncol* 2010; 28: 3582–90.
6. Voelker R. "Disappointing" trial results offer hope for older women with breast cancer. *JAMA* 2011; 305: 765–6.

Multiple myeloma. In addition to the beneficial effects of bisphosphonates on skeletal complications from bone metastases in multiple myeloma patients (see also Malignant Neoplasms of the Bone, p. 1193.2), zoledronate was reported to improve overall survival in newly diagnosed patients compared with clodronate.[1]

1. Morgan GJ, *et al.* National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 2010; 376: 1989–99.

Osteogenesis imperfecta. Bisphosphonates have been tried in osteogenesis imperfecta (p. 1167.3), but orthopaedic treatment and physical activity programmes form the basis of therapy.

Osteoporosis. Bisphosphonates are used first-line in the prevention and treatment of osteoporosis (p. 1168.1). Alendronate, risedronate and cyclical etidronate are used orally; clodronate and ibandronate have been used both orally and parenterally, and ibandronate, pamidronate, and zoledronate by intermittent intravenous infusion. Generally, in the management of **postmenopausal** osteoporosis, bisphosphonates increase bone mineral density (BMD) at both the spine and hip and reduce vertebral fractures; effect on non-vertebral fractures varies.[1,2] Treatment in women at highest risk, with prevalent fractures or low BMD, is considered most effective.[2] In the UK, NICE[3] recommends alendronate for the *primary* prevention of osteoporotic fragility fractures in women with confirmed osteoporosis; postmenopausal women below 65 years must have an independent clinical risk factor for fracture and at least one additional indicator of low BMD, women aged 65 to 69 years must have an independent clinical risk factor for fracture, and women aged 70 years or older must have an independent clinical risk factor for fracture or an indicator of low BMD. Risedronate and etidronate are recommended as alternatives in high-risk women unable to take alendronate. NICE[4] also recommends alendronate for the *secondary* prevention of osteoporotic fragility fractures in postmenopausal women with confirmed osteoporosis who have sustained a clinically apparent fracture; risedronate and etidronate are alternatives in high-risk women unable to take alendronate. Data also suggest that the more severe the osteoporosis, the greater the benefit, and since bone density continues to decline with age, and vertebral fracture incidence rises after age 75, some consider treatment more beneficial in older women.[5] However, others have expressed concern about a possible increase in brittleness of bones with long-term bisphosphonate treatment.[6]

Although there is less evidence for the efficacy of bisphosphonates for the treatment of idiopathic osteoporosis in **men**, some consider them the treatment of choice. A systematic review[7] stated that, while further evaluation of bisphosphonate therapy in **children** with secondary osteoporosis is warranted, evidence does not support their use as standard therapy.

Bisphosphonates are also considered effective at prevention and treatment of **corticosteroid-induced** osteoporosis.[8] Fracture risk (see p. 1616.2) may also be reduced although a systematic review was inconclusive in this respect.[8]

A meta-analysis of bisphosphonate use in the early **post-transplant** period found that they were effective in reducing BMD decline at the lumbar spine; however, prolonged and more intensive treatment may increase the risk of adynamic or low bone turnover disease.[9]

Bisphosphonates are also effective at increasing the BMD at the lumbar spine and hip in patients with **cystic fibrosis**, although the effect on the rate of fractures is not yet clear.[10]

1. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med* 2003; 19: 395–414.
2. Masud T, Giannini S. Preventing osteoporotic fractures with bisphosphonates: a review of the efficacy and tolerability. *Aging Clin Exp Res* 2003; 15: 89–98.
3. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 160 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA160guidance.pdf (accessed 12/01/09)
4. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 161 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA161guidance.pdf (accessed 12/01/09)
5. Dhesi JK, *et al.* The implications of a growing evidence base for drug use in elderly patients. Part 4: vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; 61: 521–8.
6. Ott S. New treatments for brittle bones. *Ann Intern Med* 2004; 141: 406–7.
7. Ward L, *et al.* Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/04/08).
8. Homik J, *et al.* Bisphosphonates for steroid induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 22/02/05).
9. Mitterbauer C, *et al.* Effects of bisphosphonates on bone loss in the first year after renal transplantation—a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; 21: 2275–81.
10. Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 22/10/10).

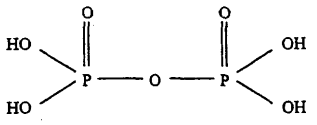
Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease.

Adverse Effects, Treatment, and Precautions

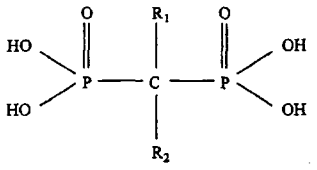
Bisphosphonates may cause gastrointestinal disturbances including abdominal pain, nausea and vomiting, and diarrhoea or constipation. Peptic ulceration has been reported. Existing gastrointestinal problems may be exacerbated, and oral bisphosphonates should generally be given with care or avoided if acute upper gastrointestinal inflammation is present. Gastrointestinal disturbances may be more frequent with aminobisphosphonates such as alendronate, ibandronate, and risedronate; oesophagitis has also occurred. General precautions to minimise the risk of oesophageal reactions, (see under Alendronate, p. 1172.3) should be observed.

Disturbances in serum electrolytes may occur, most commonly hypocalcaemia and hypophosphataemia. Existing hypocalcaemia or other disturbances of bone and mineral metabolism should be effectively treated before starting bisphosphonate therapy. Adequate intake of calcium and vitamin D is important, and supplementation may be needed if dietary intake is insufficient. Bisphos-

Figure 1. Comparative structures of the bisphosphonates.



Pyrophosphate



Generic structure of a bisphosphonate

R_1	R_2	Name
$C_3H_6.NH_2$	OH	Alendronic Acid
Cl	Cl	Clodronic Acid
CH_3	OH	Etidronic Acid
$C_2H_4.NCH_3.C_5H_{11}$	OH	Ibandronic Acid
$C_7H_{13}.NH$	H	Incadronic Acid
H	H	Medronic Acid
$CH_2.C_7H_5N_2$	OH	Minodronic Acid
$C_5H_{10}.NH_2$	OH	Neridronic Acid
H	OH	Oxidronic Acid
$C_2H_4.NH_2$	OH	Pamidronic Acid
$CH_2.C_5H_4N$	OH	Risedronic Acid
$S.C_6H_4Cl$	H	Tiludronic Acid
$CH_2.C_3H_3N_2$	OH	Zoledronic Acid

phonates may cause musculoskeletal pain (which can be severe and incapacitating), osteonecrosis of the jaw (see also Dental Care, below), ocular disturbances, and headache. Hypersensitivity reactions have occurred rarely; angioedema, rashes, urticaria, and pruritus have been reported. Other rare adverse effects include blood disorders such as anaemia, thrombocytopenia, leucopenia and disturbances in liver enzyme values.

Transient fever and flu-like symptoms have been reported, usually at the start of treatment, and are common with infusions of ibandronate, pamidronate, and zoledronate. There may be local reactions, including thrombophlebitis, after parenteral doses. Dizziness, vertigo, asthenia, peripheral oedema, paraesthesia, taste disturbances, and joint disorders have also occurred.

Impairment of renal function has been reported with bisphosphonates, particularly when given parenterally. As a result their use should generally be avoided in patients with moderate to severe renal impairment and they should be used with care in those with lesser degrees of renal impairment.

Etidronate interferes with bone mineralisation, especially at higher doses, which can result in osteomalacia and an increased incidence of fracture. Etidronate should be stopped if a fracture occurs, until healing is complete. It has also been associated with a flare in bone pain in some patients with Paget's disease. Impaired mineralisation is much less marked at usual doses of other bisphosphonates.

Overdosage with bisphosphonates would be likely to result in symptoms of hypocalcaemia; if necessary, parenteral infusion of a calcium salt could be given. Giving milk or antacids, to bind the bisphosphonate and minimise absorption, has been suggested for oral overdosage.

There is little clinical experience with bisphosphonates in pregnancy and they are generally contra-indicated; bisphosphonates have been associated with skeletal abnormalities in the fetus when given to pregnant *animals*.

Reviews.

1. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol* 2006; 17: 897–907.
2. Bobba RS, *et al.* Tolerability of different dosing regimens of bisphosphonates for the treatment of osteoporosis and malignant bone disease. *Drug Safety* 2006; 29: 1133–52.
3. Strampel W, *et al.* Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Safety* 2007; 30: 755–63.
4. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc* 2009; 84: 632–7.

Carcinogenicity. There have been infrequent reports of oesophageal cancer in patients who had taken oral bisphosphonates, particularly alendronate.[1] Some also had Barrett's oesophagus, and it has been suggested that oral bisphosphonates are contra-indicated in such patients (oral bisphosphonates should generally be used with care or avoided where acute upper gastrointestinal inflammation is present, see p. 1174.3).

Further investigation has produced conflicting results. A nested case-control study[2] using data from the UK General Practice Research Database found an increased risk of oesophageal cancer in those taking oral bisphosphonates (alendronate, etidronate, and risedronate) over an average of 7.5 years of follow-up. This increased risk was mainly restricted to those with 10 or more prescriptions or those who were treated for 3 years or more, and did not vary between the different bisphosphonates. In contrast, a cohort study[3] using the same database did not find any association between oral bisphosphonates and oesophageal cancer over 4.5 years of follow-up, although differences in design may explain the discrepancies between the 2 studies.[4]

An increased incidence of ductal carcinoma *in situ* has been reported with bisphosphonate use, see Malignant Neoplasms of the Breast, under Uses and Administration, p. 1174.2.

1. Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 2009; 360: 89–90.
2. Green J, *et al.* Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. *BMJ* 2010; 341: c4444.
3. Cardwell CR, *et al.* Exposure to oral bisphosphonates and risk of esophageal cancer. *JAMA* 2010; 304: 657–63.
4. Wysowski DK. Oral bisphosphonates and oesophageal cancer. *BMJ* 2010; 341: 516–17.

Dental care. Osteonecrosis of the jaw has been reported in patients given bisphosphonates (see p. 1176.3). Of the published cases most were associated with intravenous therapy in cancer patients, although some have followed oral therapy in patients with osteoporosis. In many cases the effect followed dental surgery. The Adverse Drug Reactions Advisory Committee in Australia has recommended that all patients scheduled to receive intravenous bisphosphonates should have a dental review,[1] and that any dental procedures be completed before beginning the drug.[1,2] Furthermore, health professionals should be aware of the presenting clinical features of osteonecrosis.[2] In the UK, the MHRA has recommended a dental review before bisphosphonate treatment in patients with cancer; other patients only require a dental review if they have poor dental status. During treatment, patients should maintain good oral hygiene, have regular check-ups, and report any oral symptoms.[3] Licensed information for some bisphosphonates has been amended in several countries to include warnings that all patients with potential risk factors for osteonecrosis of the jaw have a dental review before treatment.[4]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and osteonecrosis of the jaw. *Aust Adverse Drug React Bull* 2005; 24: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.pdf (accessed 30/11/06)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Osteonecrosis of the jaw (ONJ) with bisphosphonates. *Aust Adverse Drug React Bull* 2006; 25: 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 30/11/06)
3. MHRA/CHM. Bisphosphonates: osteonecrosis of the jaw. *Drug Safety Update* 2009; 3 (4): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0625496&RevisionSelectionMethod=LatestReleased (accessed 19/02/10)
4. Tarassoff P, Hei Y-J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; 353: 101–102. Correction. *ibid.*: 2728.

Effects on the ears. For mention of ototoxicity associated with the use of etidronate in 2 patients with pre-existing otoscierosis, and a recommendation that such patients be monitored when given bisphosphonates, see p. 1183.3. For similar effects with pamidronate, see p. 1188.1.

Effects on the eyes. Ocular effects have been associated with bisphosphonates and although reactions to pamidronate appeared to be rare, the manufacturers were aware of 23 cases up to September 1993 that were possibly associated with the drug.[1] The reactions included anterior uveitis in 7 patients and unilateral episcleritis or scleritis in 3. In one previously reported case,[2] bilateral iritis was associated with risedronate and subsequently pamidronate in a patient who had earlier received etidronate without ill-effect. There have been subsequent reports of unilateral and bilateral scleritis with pamidronate, requiring the drug to be stopped.[3] Anterior[3,4] and posterior[5] uveitis have continued to be reported, and more recently, diplopia with conjunctival swelling and eyelid oedema.[4,7] Similarly, alendronate[8-11] and zoledronate[12] have been associated with scleritis and anterior uveitis. Zoledronic acid has also been associated with orbital pain and swelling.[13] Scleritis,[14] episcleritis,[15] and uveitis[16] have also been reported with risedronate, and bilateral anterior uveitis with clodronate.[17] Non-specific conjunctivitis and abnormal or blurred vision have occurred with most of the bisphosphonates, including etidronate.[14] Dry eye, sore eye, and conjunctivitis were the most frequently reported ophthalmological events assessed as related to risedronate therapy in a prescription-event monitoring study in England.[18] The Australian Adverse Drug Reactions Advisory Committee was aware of 38 reports of serious ocular reactions to bisphosphonates as of April 2004; these were associated with pamidronate or alendronate in 18 cases each, and risedronate or zoledronate in 1 case each.[16] Most reports were of inflammatory reactions such as uveitis, iritis, scleritis, episcleritis, or optic neuritis, and occurred a median of 3 weeks after starting therapy. The risk might be higher with intravenous bisphosphonates, but the frequency of reports was thought to relate mostly to usage.[16] Acute retinal pigment epitheliitis has been reported after an intravenous infusion of zoledronate.[19] Patients who have ocular pain or vision loss while taking bisphosphonates should have the drug stopped and be referred to an ophthalmologist.[14]

1. Macarol V, Fraunfelder FT. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol* 1994; 118: 220–4.
2. Siris ES. Bisphosphonates and iritis. *Lancet* 1993; 341: 436–7.
3. Fraunfelder FW, *et al.* Scleritis and other ocular side effects associated with pamidronate disodium. *Am J Ophthalmol* 2003; 135: 219–22.
4. Rey J, *et al.* Uveitis, an under-recognized adverse effect of pamidronate: case report and literature review. *Joint Bone Spine* 2000; 67: 337–40.
5. Haverbeke G, *et al.* Posterior uveitis: an under-recognized adverse effect of pamidronate: 2 case reports. *Bull Soc Belge Ophtalmol* 2003; 290: 71–6.
6. Meaney TPJ, *et al.* Diplopia following intravenous administration of pamidronate. *Eye* 2004; 18: 103–4.
7. Ryan PJ, Sampath R. Idiopathic orbital inflammation following intravenous pamidronate. *Rheumatology (Oxford)* 2001; 40: 956–7.
8. Mbekeani JN, *et al.* Ocular inflammation associated with alendronate therapy. *Arch Ophthalmol* 1999; 117: 837–8.
9. Malik AR, *et al.* Bilateral acute anterior uveitis after alendronate. *Br J Ophthalmol* 2002; 86: 1443.
10. Salmen S, *et al.* Nongranulomatous anterior uveitis associated with alendronate therapy. *Invest Clin* 2002; 43: 49–52.
11. Asensio Sánchez VM, *et al.* Bifosfonatos e inflamación intraocular. *Arch Soc Esp Oftalmol* 2004; 79: 85–8.
12. Moore MM, Beith JM. Acute unilateral anterior uveitis and scleritis following a single infusion of zoledronate for metastatic breast cancer. *Med J Aust* 2008; 188: 370–1.
13. Sharma NS, *et al.* Zoledronic acid infusion and orbital inflammatory disease. *N Engl J Med* 2008; 359: 1410–11.
14. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. *N Engl J Med* 2003; 348: 1187–8.
15. Viñas G, *et al.* Episcleritis secundaria a risedronato. *Med Clin (Barc)* 2002; 118: 598–9.
16. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and ocular inflammation. *Aust Adverse Drug React Bull* 2004; 23: 7–8. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0404.htm (accessed 22/02/05)
17. Pietta P, *et al.* Clodronate induced uveitis. *Ann Rheum Dis* 2003; 62: 378.
18. Aurich-Barrera B, *et al.* Ophthalmological events in patients receiving risedronate: summary of information gained through follow-up in a prescription-event monitoring study in England. *Drug Safety* 2006; 29: 151–60.
19. Gilhotra JS, *et al.* Acute retinal pigment epithelitis associated with intravenous bisphosphonate. *Br J Ophthalmol* 2006; 90: 798–9.

Effects on the heart. In a study of once-yearly zoledronate for the treatment of postmenopausal osteoporosis, the number of patients who had arrhythmia in the zoledronate group was significantly higher than that in the placebo group.[1] An increased incidence of serious atrial fibrillation was also seen in the zoledronate group. Fifty patients in the zoledronate group had serious atrial fibrillation, compared with 20 patients in the placebo group. Among the 50 patients, the events occurred more than 30 days after infusion in 47 patients, by which time zoledronate would be undetectable in the circulation. The mechanism by which bisphosphonates might cause arrhythmia or atrial fibrillation is unclear; little or no effect on serum calcium concentrations was seen when measured 9 to 11 days after zoledronate infusion.

In an analysis[2] of a randomised study of alendronate in postmenopausal women with osteoporosis, 47 serious atrial fibrillation adverse events were reported in the alendronate group, compared with 31 events among those receiving placebo. There was no increased risk of all atrial fibrillation adverse events.

Although the observed association might have been due to chance,[1] it was felt that the possibility of an increased risk of atrial fibrillation with bisphosphonates should be explored.[2] Two case-control studies examining the association[3,4] came to opposite conclusions as to whether bisphosphonate treatment increased the risk of atrial fibrillation. A systematic review[5] did not find an association between bisphosphonate use (alendronate, risedronate, and zoledronate) and all atrial fibrillation events, stroke, or cardiovascular mortality; however, serious atrial fibrillation events were more common with bisphosphonates than placebo. In the UK, the MHRA stated in July 2008 that any risk appeared low and the balance of risk and benefit for bisphosphonates remained favourable.[6] The FDA in the USA examined study data for 38 045 patients who were treated with either bisphosphonates or placebo,[7] and found that atrial fibrillation was rare. Although one large study showed a significant increase in the rate of serious atrial fibrillation events, across all studies no clear association

between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was seen. Increasing dose or duration of therapy was also not associated with an increased rate of atrial fibrillation.

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Effects on the kidneys. Renal failure was associated with the intravenous use of etidronate in 2 patients with hypercalcaemia of malignancy.[1] One had been given a high dose (1 g) by short intravenous infusion on two successive days and the other had an elevated serum-creatinine concentration before treatment. A third patient given clodronate, who also developed renal failure, also had a slightly raised serum-creatinine concentration beforehand. Others[2] commented that with smaller doses of etidronate or clodronate (up to 300 mg daily) by intravenous infusion over 2 to 3 hours, renal impairment had not been seen in more than 40 patients treated. They noted a trend towards raised creatinine concentrations which was reversed when etidronate infusions were stopped. Another group[3] found increased serum-creatinine concentrations after the first infusion of etidronate when compared with placebo, but not after subsequent infusions. An overdose of parenteral etidronate led to acute renal failure in one patient.[4] Pamidronate has been associated with nephrotoxicity,[5] proteinuria,[6] acute tubular necrosis,[7,8] and collapsing focal segmental glomerulosclerosis.[9] Zoledronic acid has been associated with reports of renal impairment, occasionally after a single dose. Acute renal failure requiring dialysis or with a fatal outcome has occurred, particularly in patients with pre-existing renal impairment or other risk factors including advanced age, dehydration, or use of other nephrotoxic drugs or diuretics.[10-12] Health Canada reported that as of April 2010, Novartis had received 265 reports of renal impairment after use of one zoledronic acid preparation (*Aclasta*) corresponding to a reporting rate of about 20 cases per 100 000 patient-years of exposure.[10] Six cases of acute tubular necrosis have been reported with zoledronate;[13] all patients had received pamidronate on previous occasions, and most had mildly raised baseline serum creatinine. While pamidronate may have potentiated the renal toxicity seen with zoledronate, the authors noted that the patterns of nephrotoxicity differ between the 2 drugs. Reports to the Australian Adverse Drug Reactions Advisory Committee have suggested that renal failure or renal impairment may occur more often with zoledronate than with other bisphosphonates.[14] There has also been a report of acute renal failure with alendronate treatment in a patient with myeloma,[15] and with tiludronate in a patient treated for hypercalcaemia of malignancy.[16]

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Effects on the musculoskeletal system. Two types of musculoskeletal reactions have been reported with bisphosphonates. The FDA[1] has highlighted the possibility of severe and sometimes incapacitating bone, joint, and/or muscle pain that can occur within days, months, or years of starting bisphosphonate treatment. Symptoms may resolve quickly, slowly, or not at all after stopping the bisphosphonate. This is in contrast to the acute phase response that can occur after the first dose of an aminobisphosphonate;[2-5] arthralgia, myalgia, and bone pain are accompanied by fever, chills, fatigue, and malaise. A study to characterise the acute phase response occurring up to 3 days after zoledronate infusion found inflammatory changes in many body systems, including the joints, gastrointestinal tract, eyes, upper-respiratory tract, and possibly the skin, as well as the more non-specific symptoms of headache, fever, and fatigue.[5] Symptoms are transient and self-limiting, usually lasting 1 to 3 days, and either do not recur[2] or lessen with further doses.[4,5] Reactions were more common in younger patients, those taking NSAIDs, and those with pre-existing back pain, and less common in smokers, diabetics, those also on calcitonin, and those with previous exposure to bisphosphonates.[5] Acute phase responses are usually associated with intravenous administration, but have also occurred with oral bisphosphonates. The nitrogen-containing aminobisphosphonates seem to cause this reaction by inhibiting the mevalonate pathway, inducing the release of proinflammatory cytokines such as tumour necrosis factor α and interleukin-6.[2]

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ATYPICAL FRACTURES. A link has been suggested between prolonged alendronate treatment (usually between 1 and 10 years) and low-impact or spontaneous, non-spinal, atypical fractures.[1-6] Although most of the reported cases of such fractures have occurred in women taking alendronate, the most commonly prescribed bisphosphonate, such fractures have also been reported with ibandronate, risedronate, and zoledronate.[7] These fractures have been defined as atypical by their location in the subtrochanteric region and femoral shaft, transverse or oblique orientation, minimal or no associated trauma, and absence of comminution (breakage into several pieces). Other associated features include cortical thickening and a tendency to be bilateral.[8] Prodromal symptoms such as thigh pain, vague discomfort, and subjective weakness have been reported.[3,8] Although the oversuppression of bone turnover by the drug could explain these fractures,[1,2,9] non-adherence to bisphosphonate therapy has also been suggested as a possible cause,[9] and factors such as chronic corticosteroid use, oestrogen therapy, or parathyroid insufficiency could also contribute.[1]

In contrast to a case-control study[5] which found that prolonged bisphosphonate use for more than 5 years was associated with atypical fractures of the femoral shaft, a cohort study[10] found that patients with atypical fractures were no more likely to be on alendronate than patients with more typical osteoporotic hip fractures, and the pattern of occurrence was similar for all fracture types. Furthermore, the risk of fracture was reduced by high adherence to alendronate treatment, suggesting that the cause of atypical fractures was more likely to be osteoporosis than bisphosphonates therapy. Epidemiological studies have also shown no increased incidence of atypical fractures since bisphosphonates were approved for osteoporosis,[11] and a secondary analysis of 3 large studies found no increased risk associated with bisphosphonates even after 10 years of treatment, although the occurrence of such fractures was very rare which prevented definitive conclusions from being drawn.[7] Nonetheless, in the USA the FDA has recommended[12] that all bisphosphonates used in the treatment of osteoporosis should carry a warning of the potential risk of atypical fracture of the femur.

The management of atypical fractures thought to be associated with bisphosphonate therapy is not established. Drug holidays, once initial bisphosphonate therapy has lowered the osteoporotic fracture risk, have been considered as a possible way to reduce the risk of atypical fractures.[8,13] The positive effect bisphosphonates have on fracture risk appears to be sustained for a period after stopping treatment, and a drug holiday of between 2 to 5 years after an initial treatment period of 2 to 3 years has been suggested.[13] Although fracture healing has been reported during continued alendronate treatment,[9] some recommend stopping bisphosphonates if atypical fracture occur.[8] Patients may have delayed or absent healing even once alendronate is stopped,[1] and the associated morbidity can be high. Surgical intervention may be required.[8] Alternative treatment with the anabolic agent teriparatide may be considered,[8,14] particularly if there is little evidence of healing 4 to 6 weeks post-surgery.[8]

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OSTEONECROSIS. Osteonecrosis of the jaw has been reported with the use of some bisphosphonates.[1-4] The majority of reports have been in cancer patients treated with intravenous bisphosphonates who were also receiving chemotherapy and corticosteroids. However, osteonecrosis has also been reported in patients receiving oral bisphosphonates for osteoporosis or Paget's disease although the risk appears to be low.[5,6] Most cases have been associated with dental procedures such as tooth extraction, and many patients had local infection including osteomyelitis.[2,3] Presenting features may include altered local sensation, maxillofacial pain, toothache, denture sore spots, loose teeth, exposed bone or impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour.[3] Osteonecrosis occurs more frequently in the mandible than the maxilla;[5,6] avascular necrosis of the hip[7] and osteonecrosis of the auditory canal has also been reported.[8]

Bisphosphonate-associated osteonecrosis of the jaw has since been defined as exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks in those treated with a bisphosphonate who have not received radiotherapy to the jaw.[5,6,9] A history of dental problems, such as infection, invasive dental procedures, periodontal disease or poor dental hygiene, or the presence of dental implants or dentures may exacerbate the problem. Other possible *risk* factors include oral trauma, tobacco use, increasing age, or comorbid conditions such as diabetes or obesity.[5,6] Anti-angiogenic agents such as bevacizumab and sunitinib (see p. 748.2 and p. 859.2, respectively) may contribute to oral mucosal breakdown and subsequent development of osteonecrosis of the jaw. For recommendations on dental care in patients prescribed bisphosphonates see p. 1175.2. However, the most important risk factor for the development of osteonecrosis is considered to be bisphosphonate exposure.

Osteonecrosis occurs more frequently in patients treated with intravenous bisphosphonates than with oral. The cumulative dose is also considered to be significant, and the risk of osteonecrosis increases with the dose and duration of intravenous therapy.[5] Furthermore, the type of bisphosphonate used may affect the risk; higher potency nitrogen-containing bisphosphonates appear to present the highest risk,[5,10] and there is some suggestion that the risk may be higher with zoledronate than with pamidronate.[5] Although certain cancers, such as breast cancer and multiple myeloma, have been associated with a higher incidence of osteonecrosis,[11] the potency of the bisphosphonate, the

route used, and the cumulative dose appear to be of greater importance than the indication for treatment, and the increased risk of osteonecrosis in cancer patients is thought to be related to the higher cumulative doses given.[9,11]

Proposed *mechanisms* by which bisphosphonates induce osteonecrosis include excessive reduction of bone turnover, immunomodulation, infection, and impairment of angiogenesis.[5]

Measures for *prevention* include a pre-treatment dental exam and good dental hygiene during treatment, see Dental Care, p. 1175.2. Once osteonecrosis has developed, however, no effective treatment is known and *management* is conservative and according to severity. Control of pain and infection is important, and surgical debridement or resection of necrotic bone is used for advanced lesions.[6,9] Stopping bisphosphonate therapy does not necessarily promote healing of the necrotic process[4,10] and recovery of normal osteoclast function and bone turnover may be gradual.[12] However, some have suggested that long-term stoppage of intravenous treatment may allow lesions to stabilise and reduce symptoms, and breaks of 6 to 12 months in oral therapy may allow better resolution after debridement.[6] In 97 multiple myeloma patients who were observed for at least 3.2 years after bisphosphonate-related osteonecrosis of the jaw, osteonecrosis resolved in 62%, resolved and then recurred in 12%, and did not resolve over a follow-up period of at least 9 months in 26%.[13] Recurrence was precipitated by restarting bisphosphonate treatment or by dental procedures and could be at the same or a different site. The authors of the study suggested that multiple myeloma patients who develop osteonecrosis of the jaw after dental procedures can restart bisphosphonate therapy if skeletal-related events develop; however, patients with spontaneous osteonecrosis had a higher risk of recurrence and permanent interruption of bisphosphonate treatment may be justified. For further recommendations regarding bisphosphonate use in multiple myeloma, see Malignant Neoplasms of the Bone, under Uses and Administration, p. 1174.1.

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Effects on the respiratory system. Bronchospasm induced by bisphosphonates has been reported in 2 patients who were aspirin-sensitive asthmatics. The first patient complained of shortness of breath and wheezing 10 minutes after the start of an infusion of clodronate while the second developed similar symptoms 2 days after the start of cyclical therapy with oral etidronate. Oral rechallenge in both patients resulted in a fall in the forced expiratory values at 1 second.[1] The reaction in these 2 patients was not considered to be immune-mediated. Risedronate reportedly induced bronchiolitis obliterans organising pneumonia in a patient with sarcoidosis.[2]

For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, under Etidronate, p. 1183.3.

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Hypersensitivity. Bisphosphonates may rarely cause hypersensitivity reactions such as angioedema, urticaria, and pruritus. Reports include a severe allergic reaction to medronate disodium when given as a radiopharmaceutical,[1] and mild skin rashes in 2 patients given oral pamidronate.[2] There has also been a report of erythroderma with lesions of the mucous membranes associated with use of clodronate in one patient,[3] and severe epidermal necrosis may have been associated with tiludronate in another.[4] A possibly drug-related rash has also been reported in a patient receiving alendronate.[5] Other cutaneous reactions reported with alendronate include urticaria,[6] erythematous papules and petechiae,[7] gyrate erythema,[8] and drug-induced lichen planus;[9] licensed product information states that Stevens-Johnson syndrome has been reported. Two patients with cutaneous reactions to pamidronate or clodronate were able to continue oral clodronate after desensitisation.[10] Licensed product information states that zoledronate has been associated with rare reports of hypersensitivity, including angioedema and bronchoconstriction, and very rarely, with anaphylaxis.

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Interactions

The bisphosphonates are not well absorbed from the gastrointestinal tract, and dosage with food further impairs their absorption.

Compounds containing aluminium, calcium, iron, or magnesium, including antacids and mineral supplements and some osmotic laxatives, can also impair the absorption of bisphosphonates given orally.

It has been suggested that the use of certain bisphosphonates with NSAIDs may result in an increased incidence of gastrointestinal or renal adverse effects.

There may be additive hypocalcaemic effects with aminoglycosides.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*,[1] or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

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Pharmacokinetics

The bisphosphonates are poorly absorbed after oral doses, with bioavailabilities in the fasting state ranging from about 0.7% (alendronate; risedronate) to up to 6% (etidronate; tiludronate). Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. They have a high affinity for bone, with about 50% of an absorbed dose sequestered to ossified tissues and retained in the body for prolonged periods. Excretion is in the urine, as unchanged drug; they do not appear to be metabolised.

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Bone Morphogenetic Proteins

BMP; Proteínas morfogenéticamente óseas; Костные Морфогенетические Белки.

ATC — M05BC01 (BMP-2); M05BC02 (BMP-7).

Dibotermin Alfa *(BAN, USAN, rINN)*

Dibotermina alfa; Dibotermine Alfa; Diboterminum Alfa; hrBMP-2; rhBMP-2; Диботермин Альфа.

Human recombinant bone morphogenetic protein 2.

CAS — 246539-15-1.

ATC Vet — QM05BC01.

UNII — T472P45MG6.

Eptotermin Alfa *(BAN, rINN)*

Eptotermina alfa; Eptotermine Alfa; Eptoterminum Alfa; hrBMP-7; OP-1; Osteogenic Protein-1; Эптотермин Альфа.

Human recombinant bone morphogenetic protein 7.

CAS — 129805-33-0.

ATC Vet — QM05BC02.

UNII — IT063R5MY0.

Profile

Bone morphogenetic proteins (BMPs) are growth factors that promote ectopic bone formation and can be extracted from demineralised bone matrix. Several have been identified and developed for use in orthopaedic and reconstructive surgery; some have been produced by recombinant technology.

Eptotermin alfa is a recombinant form used in adults for the treatment of non-union of tibia of at least 9 months duration in cases where bone grafting has failed or is unfeasible. Up to a maximum of 6.6 mg eptotermin alfa may be used, the amount depending on the size of the defect. It is also used in adults with spondylolisthesis for posterolateral lumbar spine fusion where bone grafting has failed or is contra-indicated. To fuse a single level of the lumbar spine, 3.3 mg eptotermin alfa is used on each side of the spine. Dibotermin alfa, another recombinant form, is used as an adjunct to standard care for the treatment of acute tibia fractures in adults, as an implant containing up to a maximum of 24 mg. The implant is also indicated for anterior lumbar spine fusion, as a substitute for bone grafting, in adults with degenerative disc disease who have had at least 6 months of non-operative treatment. Dibotermin alfa is also used as an alternative to bone grafting for sinus augmentation, and for localised alveolar ridge augmentations for defects associated with extraction sockets. Osteogenin (BMP-3) is under investigation.

References.
1. Westerhuis RJ, *et al.* Use of bone morphogenetic proteins in traumatology. *Injury* 2005; 36: 1405–12.
2. Giannoudis PV, Tzioupis C. Clinical applications of BMP-7: the UK perspective. *Injury* 2005; 36 (suppl 3): S47–S50.
3. Wikesjö UM, *et al.* Tissue engineering with recombinant human bone morphogenetic protein-2 for alveolar augmentation and oral implant osseointegration: experimental observations and clinical perspectives. *Clin Implant Dent Relat Res* 2005; 7: 112–19.
4. Granjeiro JM, *et al.* Bone morphogenetic proteins: from structure to clinical use. *Braz J Med Biol Res* 2005; 38: 1463–73.
5. Garrison KR, *et al.* Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess* 2007; 11: 1–150.
6. Mussano F, *et al.* Bone morphogenetic proteins and bone defects: a systematic review. *Spine* 2007; 32: 824–30.

Adverse effects. The FDA issued a warning in July 2008 that use of recombinant human bone morphogenetic protein products in cervical spine fusion had been associated with at least 38 reports of swelling of neck and throat tissue, with resultant compression of the airway or vulnerable neurological structures. Complications were often life-threatening, and had required respiratory support and/or tracheotomy in some cases. The use of alternative treatments or enrollment in approved clinical studies was recommended when treating cervical spine problems.[1]

1. FDA. FDA Public Health Notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. Available at: http://www.fda.gov/cdrh/safety/070108-rhbmp.html (accessed 17/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: InductOs; ***Belg.***: InductOs; ***Cz.***: InductOs; Opgenra; Osigraft; ***Denm.***: InductOs; Opgenra; Osigraft; ***Fin.***: InductOs; ***Fr.***: InductOs; Osigraft; ***Ger.***: Opgenra; Osigraft; ***Gr.***: InductOs; Osigraft; ***Irl.***: InductOs; Opgenra; Osigraft; ***Ital.***: Osigraft; ***Neth.***: InductOs; Opgenra; Osigraft; ***Norw.***: InductOs; ***Pol.***: InductOs; Opgenra; Osigraft; ***Port.***: InductOs; Opgenra; Osigraft; ***Spain***: InductOs; Osigraft; ***Swed.***: InductOs; Osigraft; ***Switz.***: InductOs; Osigraft; ***UK***: InductOs; ***USA***: Infuse Bone Graft.

Calcitonins

Calcitoninas.

ATC — H05BA01 (salmon synthetic); H05BA02 (pork natural); H05BA03 (human synthetic).

ATC Vet — QH05BA01 (salmon synthetic); QH05BA02 (pork natural); QH05BA03 (human synthetic).

Calcitonin (Human)

Calcitonina (humana); Calcitonin-human; Human Calcitonin.
$C_{151}H_{228}N_{40}O_{45}S_2$=3417.9
CAS — 21215-62-3.
ATC — H05BA03 (human synthetic).
ATC Vet — QH05BA03 (human synthetic).
UNII — K0O929019.

Description. Calcitonin (human) is a synthetic polypeptide comprising 32 amino acids in the same linear sequence as in naturally occurring human calcitonin.

Calcitonin (Pork) *(BANM)*

Calcitonina (cerdo); Calcitonina porcina.
CAS — 12321-44-7.
ATC — H05BA02 (pork natural).
ATC Vet — QH05BA02 (pork natural).
UNII — A38SN5VGB4.

NOTE. The synonym thyrocalcitonin and the CAS number 9007-12-9 have been used for calcitonin that is often of pork origin.

Description. Calcitonin (pork) is a polypeptide hormone obtained from pork thyroid.

Calcitonin (Salmon) *(BAN)*

Calcitonin (Lachs); Calcitonina (salmón); Calcitonin-salmon; Calcitoninum salmonis; Kalcitonin lososí; Kalcytonina łososiowa; Kalsitoniini (lohi); Kalsitonin (Somon); Lašišų kalcitoninas; Laxkalcitonin; Lazac-kalcitonin; Salcatonin; Salcatonina; Salkatonin; Salmon Calcitonin; SCT-1; SMC-20-051.
$C_{145}H_{240}N_{44}O_{48}S_2$=3431.9
CAS — 47931-85-1.
ATC — H05BA01 (salmon synthetic).
ATC Vet — QH05BA01 (salmon synthetic).
UNII — 7SFC6U2V15.

Nomenclature. There may be some confusion between the terms Salcatonin and Calcitonin (Salmon) (Salmon Calcitonin; Calcitonin-salmon) although in practice these names appear to be used for the same substance.

- The Ph. Eur. 8 defines Calcitonin (Salmon) as a polypeptide having the structure determined for salmon calcitonin I. It is available as an acetate.
- Calcitonin (Salmon)/Salcatonin (*BAN*) is defined as a *component* of natural salmon calcitonin. The BP 2014 defines Calcitonin (Salmon)/Salcatonin as a synthetic polypeptide having the structure determined for salmon calcitonin I.
- In the USA, Calcitonin (*USAN*) includes calcitonin (human) and calcitonin (salmon) and there Salcatonin is understood to be a synthetic polypeptide structurally similar to natural salmon calcitonin (Calcitonin Salmon (Synthesis)). The US manufacturers use Calcitonin-salmon for a synthetic polypeptide with the same structure as calcitonin of salmon origin.

The names Ostora and Capsitonin have been used as trade marks for oral calcitonin (salmon).

Pharmacopoeias. In *Chin*, *Eur.* (see p. vii), and *US*..

Ph. Eur. 8: (Calcitonin (Salmon)). A white or almost white powder. It is obtained by chemical synthesis or by a method based on recombinant DNA (rDNA) technology. Freely soluble in water. Store at 2 degrees to 8 degrees. If the substance is sterile store in a sterile, airtight, tamper-proof container. Protect from light.

USP 36: (Calcitonin Salmon). It is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. 1 mg of acetic acid-free, anhydrous calcitonin salmon is equivalent to 6000 USP units. Store in airtight containers at a temperature of 2 degrees to 8 degrees, or maintain in a frozen state. Protect from light.

Elcatonin *(rINN)*

Carbocalcitonin; Elcatonina; Elcatonine; Elcatoninum; [Aminosuberic Acid 1,7]-eel Calcitonin; [Asu^{1,7}]-E-CT; Элькатонин.
1-Butyric acid-7-(L-2-aminobutyric acid)-26-L-aspartic acid-27-L-valine-29-L-alaninecalcitonin (salmon).
$C_{148}H_{244}N_{42}O_{47}$=3363.8
CAS — 60731-46-6.
ATC — H05BA04.
ATC Vet — QH05BA04.
UNII — W0CM5474JK.

Description. Elcatonin is a synthetic analogue of eel calcitonin.

Pharmacopoeias. In *Jpn*.

Incompatibility. Like some other peptide drugs, calcitonin may be adsorbed onto the plastic of intravenous giving sets; it has been suggested that solutions for intravenous infusion should contain some protein to prevent the sorption and consequent loss of potency (see under Administration, below).

Units

0.8 units of calcitonin, porcine, are contained in one ampoule of the second International Standard Preparation (1991).

128 units of calcitonin, salmon, are contained in approximately 20 micrograms of freeze-dried purified synthetic salmon calcitonin, with mannitol 2 mg in one ampoule of the second International Standard Preparation (1989).

17.5 units of calcitonin, human, are contained in one ampoule of the second International Standard Preparation (1991).

88 units of calcitonin, eel, are contained in one ampoule of the first International Standard Preparation (1989).

Potency of calcitonins is estimated by comparing the hypocalcaemic effect, in *rats*, with that of the standard preparation, and is expressed in international or MRC units which are considered to be equivalent. One manufacturer states that 100 international units by this assay is equivalent to 1 mg of porcine or human calcitonin, and to 25 micrograms of salmon calcitonin although other, slightly different, equivalencies have been cited for other preparations. However, although 1 unit of pork calcitonin, 1 unit of salmon calcitonin, and 1 unit of human calcitonin should give the same response in humans this is not necessarily the case. Doses of calcitonin that have been considered approximately equivalent in practice are:

- 80 units of pork calcitonin
- 50 units of salmon calcitonin
- 500 micrograms of human calcitonin

Clinically, doses of pork and salmon calcitonin are expressed in units whereas those of human calcitonin can be expressed by weight, probably a reflection of its purity.

Uses and Administration

Calcitonin is a hormone produced by mammalian thyroid parafollicular cells or the ultimobranchial gland in non-mammalian vertebrates. In man its secretion and biosynthesis are regulated by the plasma-calcium concentration. It has a hypocalcaemic action that is due primarily to inhibition of osteoclastic bone resorption; of less importance is a direct effect on the kidneys resulting in increased urinary excretion of calcium and phosphorus. Calcitonin contains 32 amino acids; the sequence varies according to the species. Synthetic calcitonin (salmon) is most commonly used in practice; it is the most potent and has the longest duration of action. Naturally occurring calcitonin (pork) has been used, and synthetic calcitonin (human) and elcatonin (a synthetic derivative of eel calcitonin) are available in some countries.

Calcitonins are used in the treatment of diseases characterised by high bone turnover such as Paget's disease of bone. They are also given as an adjunct in the treatment of severe hypercalcaemia, especially that associated with malignancy, and in the prevention of acute bone loss due to sudden immobilisation such as in osteoporotic fractures. In some countries calcitonins are used in the management of postmenopausal osteoporosis; however, the EMEA recommended against such use due to the increased risk of cancer with long-term treatment (see Carcinogenicity, p. 1179.2) and restricted their use in other conditions (see below).

Calcitonins are generally given by subcutaneous or intramuscular injection; some have been given intranasally, rectally, or by intravenous infusion or slow intravenous injection.

In **Paget's disease of bone** the usual dose range for calcitonin (salmon) is 50 units three times weekly to 100 units daily by subcutaneous or intramuscular injection. Calcitonin (human) is usually given by subcutaneous or intramuscular injection; doses range from 500 micrograms two to three times weekly, to 250 or 500 micrograms daily; severe cases may require up to 1 mg daily in 2 divided doses. In the EU, such use of calcitonin is restricted to patients who do not respond to, or are intolerant of, other therapy and duration of treatment is limited to 3 months (or 6 months in exceptional circumstances).

As an adjunct to the treatment of **hypercalcaemia**, calcitonins have a rapid effect which is greatest in patients with an increased bone turnover. Calcitonin (salmon) may be given by subcutaneous or intramuscular injection in a dose of 4 units/kg every 12 hours, increased if necessary after one or two days to 8 units/kg every 12 hours, up to a maximum of 8 units/kg every 6 hours after a further two days. Alternatively, 100 units every 6 to 8 hours may be given, increased after one or two days to a maximum of 400 units every 6 to 8 hours. In the emergency treatment of hypercalcaemic crisis, calcitonin (salmon) has also been given intravenously: a suggested dose is up to 10 units/kg diluted in 500 mL of sodium chloride 0.9% and given by slow intravenous infusion over at least 6 hours (see also Administration below for the problems of intravenous dosage). Calcitonin (human) 500 micrograms every 6 hours has also been given by slow intravenous injection for hypercalcaemia of malignancy.

Calcitonin (salmon) is also used for the **prevention of acute bone loss** due to sudden immobilisation such as in patients with recent osteoporotic fractures. The recommended dose is 100 units once daily (or 50 units twice daily) by subcutaneous or intramuscular injection, for 2 to 4 weeks only; the dose may be reduced to 50 units daily at the start of remobilisation.

In the USA, calcitonin (salmon) is used in the treatment of **postmenopausal osteoporosis** in a dose of 200 units daily intranasally by nasal spray, alternating nostrils each day. A subcutaneous or intramuscular dose of 100 units every other day has been suggested. Supplementary calcium (equivalent to at least 600 mg of elemental calcium daily) and vitamin D (400 units daily) should also be given.

For details of administration in renal impairment, see below.

Calcitonin (salmon) has also been used for the control of **bone pain due to malignant neoplasms** although in the EU such use is no longer considered appropriate.

Oral formulations of calcitonin (salmon) are being studied.

Administration. Calcitonins have poor oral bioavailability and are usually given by subcutaneous or intramuscular injection. To improve patient acceptability, especially in diseases requiring long-term drug therapy, alternative routes have been investigated:[1]

- calcitonin (salmon) has proved effective when given **intranasally** in usual doses of 50 to 200 units daily (for references, see Osteoporosis p. 1179.1), and intranasal products for osteoporosis are available in some countries.
- suppositories containing 300 units of calcitonin (salmon) have been used **rectally** in the management of hypercalcaemia; one suppository being given three times daily (total daily dose of 900 units).[2,3] Daily doses of 100 units of calcitonin (salmon) by suppository have been tried in postmenopausal osteoporosis[4] and in patients with bone pain.[5]
- calcitonins have been given by **intravenous infusion**, but this is rarely necessary and may cause more adverse effects. If intravenous use is essential, it has been suggested[6] that some protein must be present in the solution to prevent adsorption onto the plastic of the giving set. However, in practice this does not seem to be the case; in the UK, manufacturer's recommendations are for dilution with normal saline, while acknowledging that such dilution results in a loss of potency, and dosage is adjusted accordingly. Presumably dilution with a protein-containing solution would allow lower doses to be used. The manufacturers do specify that solutions for infusion should be prepared immediately before use and that glass or hard plastic containers should not be used.

Novel formulations of an orally active calcitonin have been investigated; one such formulation using a low-molecular-weight carrier, was considered effective and well-tolerated in early studies.[7,8]

1. Inzerillo AM, *et al.* Calcitonin: physiological actions and clinical applications. *J Pediatr Endocrinol Metab* 2004; 17: 931–40.
2. Thiébaud D, *et al.* Effectiveness of salmon calcitonin administered as suppositories in tumor-induced hypercalcemia. *Am J Med* 1987; 82: 745–50.
3. Thiébaud D, *et al.* Fast and effective treatment of malignant hypercalcemia: combination of suppositories of calcitonin and a single infusion of 3-amino 1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990; 150: 2125–8.
4. Gonnelli S, *et al.* Effect of rectal salmon calcitonin treatment on bone mass and bone turnover in patients with established postmenopausal osteoporosis: a 1-year crossover study. *Curr Ther Res* 1993; 54: 458–65.
5. Mannarini M, *et al.* Analgesic effect of salmon calcitonin suppositories in patients with bone pain. *Curr Ther Res* 1994; 55: 1079–83.
6. Stevenson JC. Current management of malignant hypercalcaemia. *Drugs* 1988; 36: 229–38.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; 17: 1478–85.
8. Tankó LB, *et al.* Safety and efficacy of a novel salmon calcitonin (sCT) technology-based oral formulation in healthy postmenopausal women: acute and 3-month effects on biomarkers of bone turnover. *J Bone Miner Res* 2004; 19: 1531–8.

Administration in renal impairment. Calcitonins are metabolised mainly in the kidneys and pharmacokinetic studies (see p. 1179.3) have indicated that the dosage of calcitonins may need to be reduced in patients with renal insufficiency, but there have been no specific guidelines.

Charcot neuroarthropathy. In a small study in patients with acute Charcot neuroarthropathy, intranasal calcitonin with calcium supplementation significantly reduced

bone turnover compared with calcium supplementation alone.[1]

1. Bem R, *et al.* Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. *Diabetes Care* 2006; 29: 1392–4.

Hypercalcaemia. Calcitonins can be used in addition to rehydration and diuresis in the management of moderate to severe symptomatic hypercalcaemia (p. 1778.1), including that of malignancy (p. 1167.2). Because of their rapid effect, they may be particularly useful in life-threatening hypercalcaemia. However, although they have a rapid effect it is usually short-lived; calcitonins are therefore generally given as an adjunct with other therapy such as a bisphosphonate.

Malignant neoplasms of the bone. Calcitonins may be useful adjuvants in the treatment of malignant disease involving the bone, not only to correct hypercalcaemia of malignancy (p. 1167.2), but perhaps to relieve bone pain and osteolysis. A systematic review[1] concluded however that available evidence did not support the use of calcitonin for metastatic bone pain; the review was limited to only a few studies. Other therapeutic measures were recommended until further studies are done. In the EU, the use of injectable calcitonins for metastatic bone pain is no longer recommended.

1. Martinez-Zapata MJ, *et al.* Calcitonin for metastatic bone pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/04/08).

Osteogenesis imperfecta. There have been reports[1,2] of beneficial effects with calcitonins in the treatment of osteogenesis imperfecta (p. 1167.3), but their use has declined in favour of bisphosphonates.

1. Castells S, *et al.* Therapy of osteogenesis imperfecta with synthetic salmon calcitonin. *J Pediatr* 1979; 95: 807–11.
2. Nishi Y, *et al.* Effect of long-term calcitonin therapy by injection and nasal spray on the incidence of fractures in osteogenesis imperfecta. *J Pediatr* 1992; 121: 477–80.

Osteoporosis. Calcitonins may be used in the treatment of **postmenopausal** osteoporosis (p. 1168.1). Long-term use of calcitonins has been associated with an increased risk of cancer and they are not recommended for postmenopausal osteoporosis in the EU (for further details see Carcinogenicity, under Adverse Effects, below); however, such use may still be permitted in other countries. They are usually second-line agents; however, because of their analgesic effect, they may be useful for the initial treatment of those with bone pain due to vertebral crush fractures.[1] Calcitonin (salmon) nasal spray has been shown to significantly reduce the risk of vertebral fractures in women with established osteoporosis,[2] although the study has been criticised[3] for a high drop-out rate. Any effect on hip fracture is unestablished.[1,2]

Calcitonins have also been tried in the prevention and treatment of other types of osteoporosis. In the management of **corticosteroid**-induced osteoporosis, they appear to maintain bone mineral density (BMD) at the lumbar spine, but not at the femoral neck. Effects on prevention of fractures have not been established.[1,4] Nasal calcitonin (salmon) has been found to increase lumbar spine BMD in **men** with idiopathic osteoporosis.[1]

1. Silverman SL. Calcitonin. *Endocrinol Metab Clin North Am* 2003; 32: 273–84.
2. Chesnut CH, *et al.* A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med* 2000; 109: 267–76.
3. Cummings SR, Chapurlat RD. What PROOF proves about calcitonin and clinical trials. *Am J Med* 2000; 109: 330–1.
4. Cranney A, *et al.* Calcitonin for preventing and treating corticosteroid-induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 22/02/05).

Paget's disease of bone. Calcitonins may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. However, the bisphosphonates have largely superseded the calcitonins in this role.

Pain. In addition to bone pain associated with malignancy and with bone disorders such as Paget's disease, calcitonins may also have other analgesic properties. Beneficial results have been seen in various painful conditions, including complex regional pain syndrome (p. 8.1), and particularly with intranasal salmon calcitonin.[1] Salmon calcitonin 100 or 200 units intravenously has also provided relief[2] from phantom limb pain (p. 10.3) after amputation. A small double-blind crossover study of intravenous calcitonin in amputee patients with phantom limb pain found it was ineffective, however, in contrast to ketamine.[3] Intranasal calcitonin at a dose of 200 units also provided only transient relief of phantom limb sensation after spinal cord injury in a patient refractory to clomipramine;[4] the authors speculated that optimal dosage may not have been used and noted that all previous studies were in amputees.

For a discussion on pain and its management, see p. 4.1.

1. Appelboom T. Calcitonin in reflex sympathetic dystrophy syndrome and other painful conditions. *Bone* 2002; 30 (suppl): 84S–86S.
2. Wall GC, Heyneman CA. Calcitonin in phantom limb pain. *Ann Pharmacother* 1999; 33: 499–501.
3. Eichenberger U, *et al.* Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* 2008; 106: 1265–73.
4. Shapiro S, *et al.* Calcitonin treatment for phantom limb pain. *Can J Psychiatry* 2004; 49: 499.

Adverse Effects, Treatment, and Precautions

Calcitonins may cause nausea, vomiting, diarrhoea, dizziness, flushing, and tingling of the hands. These reactions are dose dependent, usually transient, and occur more often with intravenous doses. Nausea and vomiting may be reduced by giving doses at bedtime and after meals, or by giving an antiemetic beforehand. Other adverse effects have included rash, an unpleasant taste, abdominal pain, urinary frequency, tremor, oedema, headache, flu-like symptoms, visual disturbances, pruritus, musculoskeletal pain including arthralgia, hypertension, and fatigue. A diabetogenic effect has been reported rarely. Inflammatory reactions at the injection site have been reported with some calcitonins. Transient hypocalcaemia may occur after injections of calcitonin, and use is contra-indicated in patients with hypocalcaemia. The most commonly reported adverse effects associated with intranasal calcitonin are nasal discomfort, rhinitis, sinusitis, and epistaxis. Nasal ulcers may develop and intranasal calcitonin should be withheld until small ulcers heal, or withdrawn for severe ulceration.

Calcitonins should be given with care to patients with renal impairment or heart failure. If children receive calcitonin it should preferably be for short periods and bone growth should be monitored.

Circulating antibodies may develop after several months of use but resistance does not necessarily follow (see also Antibody Formation, below). Serious hypersensitivity reactions have occurred rarely and include bronchospasm, swelling of the tongue and throat, and anaphylactic shock which has occasionally been fatal. Allergic reactions should be differentiated from non-allergic flushing and hypotension. A skin test is advised before use if hypersensitivity is suspected.

Long-term use of calcitonin has been associated with an increased risk of cancer, see Carcinogenicity, below.

Calcitonin has inhibited lactation in *animals*.

Calcitonin (pork) may contain trace amounts of thyroid hormones, but clinical effects are unlikely in most patients.

Antibody formation. Long-term treatment with heterologous calcitonins may lead to the formation of neutralising antibodies. This appears to be common in patients given calcitonin (pork) or, to a lesser extent, calcitonin (salmon). Calcitonin (human) is less immunogenic than pork or salmon, but a study[1] has also detected antibodies to human calcitonin in 1 of 33 women with postmenopausal osteoporosis after 6 months of therapy.

The degree to which such antibodies affect therapeutic activity is uncertain. Some studies have suggested a significant loss of therapeutic activity in patients who developed neutralising antibodies to calcitonin (salmon),[2] or a restoration in activity after a switch from salmon to human calcitonin in such patients;[3] equally, others have presented evidence that the activity of calcitonin (salmon) was not reduced by the development of antibodies to the drug.[4]

1. Grauer A, *et al.* Formation of neutralizing antibodies after treatment with human calcitonin. *Am J Med* 1993; 95: 439–42.
2. Grauer A, *et al.* In vitro detection of neutralizing antibodies after treatment of Paget's disease of bone with nasal salmon calcitonin. *J Bone Miner Res* 1990; 5: 387–91.
3. Muff R, *et al.* Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990; 89: 181–4.
4. Reginster JY, *et al.* Influence of specific anti-salmon calcitonin antibodies on biological effectiveness of nasal salmon calcitonin in Paget's disease of bone. *Scand J Rheumatol* 1990; 19: 83–6.

Carcinogenicity. In 2012, an EMEA review[1,2] of all available data on calcitonin found an increased risk of cancer of various types with long-term use that varied between 0.7% in studies using an unlicensed oral formulation to 2.4% in studies using intranasal formulations. It was recommended that all formulations of calcitonin should no longer be used for the treatment of postmenopausal osteoporosis and that intranasal formulations be withdrawn in the EU; treatment of other conditions should be limited to the shortest possible time using the smallest effective dose, see Uses and Administration, p. 1178.2.

1. EMEA. Press release: European Medicines Agency recommends limiting long-term use of calcitonin medicines (issued 20th July, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/07/WC500130122.pdf (accessed 30/10/12)
2. EMEA. Questions and answers on the review of calcitonin-containing medicines (issued 19th July, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Calcitonin_31/WC500130149.pdf (accessed 30/10/12)

Effect on glucose metabolism. A single subcutaneous injection of calcitonin (salmon) has been reported to increase blood-glucose concentrations,[1] but long-term treatment with calcitonins was considered unlikely to cause diabetes.[2] Nevertheless, deterioration in diabetic control has been noted in a patient given calcitonin (pork) [3] and postprandial release of insulin was abolished by intravenous salmon calcitonin in 8 patients with duodenal ulcers.[4]

1. Gantereau A, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1977; ii: 1076–7.
2. Evans IMA, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1978; i: 280.
3. Thomas DW, *et al.* Deterioration in diabetic control during calcitonin therapy. *Med J Aust* 1979; 2: 699–70.
4. Jonderko K. Effect of calcitonin on gastric emptying in patients with an active duodenal ulcer. *Gut* 1989; 30: 430–5.

Gynaecomastia. A 62-year-old man developed painful gynaecomastia on two occasions after treatment with calcitonin (salmon) given by subcutaneous injection.[1]

1. Vanikrunkelsven PJ, Thijs MM. Salcatonin and gynaecomastia. *Lancet* 1994; 344: 482.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcitonin (salmon) as probably not porphyrinogenic based on a report of uneventful use in one patient with acute porphyria; it may be used as a drug of first choice and no precautions are needed. Calcitonin (pork), calcitonin (human), and elcatonin are not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

There is a theoretical possibility that dosage adjustments of cardiac glycosides or calcium-channel blockers may be required in patients who are given injections of calcitonin, because of the effects of the latter on serum calcium.

Pharmacokinetics

Calcitonins are rapidly inactivated when given orally. After injection, calcitonins are quickly metabolised, primarily in the kidneys but also in blood and peripheral tissues. Bioavailability has been reported to be about 70%; plasma protein binding is about 30 to 40%. The inactive metabolites and a small proportion of unchanged drug are excreted in the urine. The elimination half-life after injection of calcitonin (human) is stated to be 60 minutes and that of calcitonin (salmon) about 70 to 90 minutes.

Calcitonins are also absorbed through the nasal and rectal mucosa. Although figures have varied widely, about 3% of an intranasal dose of calcitonin (salmon) is reported to be bioavailable compared with the same dose given by intramuscular injection, with peak plasma concentrations occurring after about 30 to 40 minutes compared with 15 to 25 minutes after the parenteral dose. Elimination half-life has been reported to be about 16 to 43 minutes.

After the *subcutaneous injection* of 19.9 micrograms of synthetic calcitonin (salmon) in 16 healthy subjects,[1] absorption was rapid with an absorption half-life of 23.4 minutes. The maximum mean plasma concentration was 384 picograms/mL at 60 minutes after which excretion was fairly rapid with an elimination half-life of 87 minutes. These results and those from previously reported investigations of salmon, human, and porcine calcitonin could not easily be compared, especially since different assay methods had been used. Nevertheless it was concluded that bioavailability from subcutaneous and intramuscular injection sites was good; that dosage may need to be adjusted in renal insufficiency because of low metabolic clearance rate; and that the higher potency of calcitonin (salmon) is due to higher intrinsic activity at the receptor site rather than to pharmacokinetic differences. The US manufacturers have cited a half-life of 1.02 hours after a single subcutaneous injection of calcitonin (human) 500 micrograms. The plasma elimination half-life of elcatonin was about 4.8 hours after *intramuscular injection* in healthy subjects.[2]

Calcitonins are absorbed on *intranasal* or *rectal* dosage. Peak plasma concentrations of calcitonin (salmon) were achieved after 20 to 60 minutes when given by nasal spray in doses ranging from 200 to 400 units.[3] In another study[4] calcitonin (salmon) 200 units, repeated once after 3 hours, was given by nasal spray or suppository to healthy subjects. Absorption was prompt and the total amount absorbed was similar with either route. However, whereas intranasal dosage produced low peaks with calcitonin (salmon) still detectable in the blood after 3 to 5 hours, rectal dosage produced peak plasma concentrations about 6 to 8 times higher but the drug was undetectable within 2 hours; plasma concentrations were lower than those found after injection. Another group[5] found calcitonin (human) to be poorly absorbed when given intranasally to healthy

subjects. Absorption from nasal powder or spray solutions was improved by the presence of the surfactants dihydrofusinate or glycocholate.

Investigations carried out in 4 osteoporotic patients[6] suggested that the rectal calcitonin (salmon) could provide 65% of the bioavailability of intramuscular doses.

A study of an *oral* formulation of calcitonin (salmon) in healthy subjects evaluated different oral doses in comparison to intravenous dosing, and found 1.2 mg orally to be comparable to 10 micrograms intravenously, in terms of bioavailability and efficacy.[7]

1. Nüesch E, Schmidt R. Comparative pharmacokinetics of calcitonins. In: Pecile A, ed. *Calcitonin international congress series no. 540*. Amsterdam: Excerpta Medica, 1980: 352–64.
2. Segre G, *et al.* Pharmacokinetics of carbocalcitonin in humans. *Clin Trials J* 1986; **23** (suppl 1): 23–8.
3. Kurose H, *et al.* Intranasal absorption of salmon calcitonin. *Calcif Tissue Int* 1987; **41**: 249–51.
4. Buclin T, *et al.* The effect of rectal and nasal administration of salmon calcitonin in normal subjects. *Calcif Tissue Int* 1987; **41**: 252–8.
5. Pontiroli AE, *et al.* Nasal administration of glucagon and human calcitonin to healthy subjects: a comparison of powders and spray solutions and of different enhancing agents. *Eur J Clin Pharmacol* 1989; **37**: 427–30.
6. Gennari C, *et al.* Pharmacodynamic activity of synthetic salmon calcitonin in osteoporotic patients: comparison between rectal and intramuscular administration: pilot study. *Curr Ther Res* 1993; **53**: 301–8.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17**: 1478–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Miacalcic; ***Austria***: Ucecal; ***Belg.***: Calsynar†; Miacalcic; Steocalcin†; ***Braz.***: Acticalcin; Calsynar; Miacalcic; Seacalcit; Serocalcin†; ***Canad.***: Calcimar; Caltine; Miacalcin; ***Chile***: Calnisan†; Miacalcic; ***China***: Bang Rui De (邦瑞得); Calco (考克); Da Fen Gai (达芬盖); Elcitonin (益盖宁); Gai Rui Ning (盖瑞宁); Gu Tai Ning (固泰宁); Han Xin (翰欣); Jin Er Li (金尔力); Miacalcic (密盖息); Si Di Nuo (斯迪诺); ***Cz.***: Miacalcic; Osteodon†; Tonocalcin; ***Denm.***: Miacalcic; ***Fin.***: Miacalcic; ***Fr.***: Cadens; Calsyn; Cibacalcine†; Miacalcic; ***Ger.***: Calci†; Karil†; ***Gr.***: Alciton; Alfaton; Alicitonin; Arsipor; Assocals; Aurocalcin; Brosidon; Calc-Up; Calci-10; Calcicontrol; Calcideron; Calciphar; Calciplus; Calcispren; Calcitherapy; Calciton; Calco; Calcytonil; Caloston; Calsal; Calsaton; Calsynar; Caltec; Cibacalcin; Crocalcin; Doctadryle; Farmicalcine; Galcin; Genecalcin; Iamacalcin; Iricalcin; Latonina; Lixocam; Miacalcic; Miadenil; Mioser; Myocal; Neostesin; Nopremin; Norcalcin; Nylex; Osanit; Osivan; Osteonorm; Osticalcin; Ostifix; Ostoplus; Ostosalm; Pluston; Rafacalcin; Redicalcin; Rothrin; Sal-Cal; Salcatol; Salmocalcin; Salmofar; Salmoten; Sanopor; Steocin; Tendolon; Tonocalcin; Tosicalcin; Transcalcium; Ucecal; Velkacalcin; Zyoston; ***Hong Kong***: Miacalcic; ***Hung.***: Biostin†; Calco; Miacalcic; ***India***: Biocalcin; Calcinase; Calsynar; Miacalcic; Ostospray; Zycalcit; ***Indon.***: Miacalcic; Tonocalcin; ***Irl.***: Miacalcic; Miakaril; Ostulex; ***Israel***: Fortical; Miacalcic; Salco; ***Ital.***: Calcitonina; Salmofar†; ***Jpn***: Calcitoran; Elcitonin; ***Malaysia***: Miacalcic; Tendolon; ***Mex.***: Miacalcic; Oseum; ***Neth.***: Forcaltonin†; ***Norw.***: Miacalcic; ***NZ***: Miacalcic; ***Philipp.***: Miacalcic; ***Pol.***: Calcihexal†; Calcitonin; Miacalcic; Tonocalcin; ***Port.***: Calcitart†; Calsyn; Miacalcic; Osseocalcina; Osteodon; Ostinate; Salcat; Tonocaltin; ***Rus.***: Alostin (Алостин); Miacalcic (Миакальцик); Osteover (Остеовер); ***S.Afr.***: Miacalcic; ***Singapore***: Miacalcic; ***Spain***: Calogen†; Calsynar; Carbicalcin; Diatin†; Fosatur†; Miacalcic; Oseototal†; Osport†; Osteobion†; Ostetan†; Tonocaltin†; ***Swed.***: Miacalcic; ***Switz.***: Miacalcic; ***Thai.***: Cadotin; Calci-10; Calco; Miacalcic; Mycalcin; Salmocin; Tonocalcin; ***Turk.***: Biocalcin; Calcitonina; Calsynar; Miacalcic; Salmocalcin; Strabone; Tonocalcin; Ucecal; ***UK***: Miacalcic; ***Ukr.***: Miacalcic (Миакальцик); ***USA***: Calcimar; Fortical; Miacalcin; Osteocalcin.

Pharmacopoeial Preparations
BP 2014: Calcitonin (Salmon) Injection;
USP 36: Calcitonin Salmon Injection; Calcitonin Salmon Nasal Solution.

Cinacalcet Hydrochloride

(BANM, USAN, rINNM)

AMG-073 (cinacalcet); Cinacalcet, Chlorhydrate de; Cinacalcet, hidrocloruro de; Cinacalceti Hydrochloridum; Hidrocloruro de cinacalcet; KRN-1493; Цинакальцета Гидрохлорид.

N-[(1*R*)-1-(Naphthalen-1-yl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine hydrochloride.

$C_{22}H_{22}F_3N.HCl=393.9$

CAS — 364782-34-3.
ATC — H05BX01.
ATC Vet — QH05BX01.
UNII — 1K860WSG25.

Uses and Administration

Cinacalcet is a calcimimetic agent that increases the sensitivity to extracellular calcium of the calcium-sensing receptors of the parathyroid gland, which regulate parathyroid hormone secretion; this results in a reduction in parathyroid hormone secretion as well as a decrease in serum calcium. Cinacalcet hydrochloride is given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, as well as for the reduction of hypercalcaemia in patients with parathyroid carcinoma or primary hyperparathyroidism (where parathyroidectomy is not an option). Doses are expressed in terms of the base; cinacalcet hydrochloride 33 mg is equivalent to about 30 mg of cinacalcet.

In the treatment of **secondary hyperparathyroidism**, the initial dose is 30 mg once daily, increased at intervals of 2 to 4 weeks by 30 mg to a maximum of 180 mg daily.

For the treatment of **hypercalcaemia** in patients with parathyroid carcinoma or primary hyperparathyroidism, cinacalcet is given in an initial dose of 30 mg twice daily, increased sequentially at intervals of 2 to 4 weeks to a maximum of 90 mg three or four times daily.

References.
1. Franceschini N, *et al.* Cinacalcet HCl: a calcimimetic agent for the management of primary and secondary hyperparathyroidism. *Expert Opin Invest Drugs* 2003; **12**: 1413–21.
2. Shoback DM, *et al.* The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88**: 5644–9.
3. Block GA, *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; **350**: 1516–25.
4. Joy MS, *et al.* Calcimimetics and the treatment of primary and secondary hyperparathyroidism. *Ann Pharmacother* 2004; **38**: 1871–80.
5. Peacock M, *et al.* Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90**: 135–41.
6. Barman Balfour JA, Scott LJ. Cinacalcet hydrochloride. *Drugs* 2005; **65**: 271–81.
7. Cunningham J, *et al.* Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68**: 1793–1800.
8. Dong BJ. Cinacalcet: an oral calcimimetic agent for the management of hyperparathyroidism. *Clin Ther* 2005; **27**: 1725–51.
9. NICE. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy: Technology Appraisal Guidance 117 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA117guidance.pdf (accessed 18/04/08)
10. Drüeke TB, Ritz E. Treatment of secondary hyperparathyroidism in CKD patients with cinacalcet and/or vitamin D derivatives. *Clin J Am Soc Nephrol* 2009; **4**: 234–41.

Administration in hepatic impairment. For precautions when using cinacalcet in those with hepatic impairment, see below.

Adverse Effects and Precautions

Hypocalcaemia and adynamic bone disease can occur; serum calcium and intact parathyroid hormone concentrations should be monitored regularly, especially in patients with a history of seizure disorders or hepatic impairment. A reduction in free testosterone concentrations has also been reported during treatment. Other adverse effects of cinacalcet include gastrointestinal disturbances, myalgia, dizziness, paraesthesia, seizures, hypertension, asthenia, anorexia, rashes, and non-cardiac chest pain. There have been isolated reports of hypotension, worsening heart failure, or both, in patients with impaired cardiac function. Hypersensitivity reactions including angioedema and urticaria have been reported. Plasma concentrations of cinacalcet may be increased in patients with moderate to severe hepatic impairment, and caution and close monitoring are advised.

Interactions

Cinacalcet is partly metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Concentrations of cinacalcet have almost doubled when given with the CYP3A4 inhibitor ketoconazole. Dose adjustments of cinacalcet may be required if therapy with strong inhibitors or inducers of CYP3A4 is started, or stopped. Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism, and dose adjustments may be necessary if patients start or stop smoking. Cinacalcet is a strong inhibitor of cytochrome P450 isoenzyme CYP2D6; exposure to amitriptyline, desipramine, and nortriptyline has been increased when given with cinacalcet.

Pharmacokinetics

Peak plasma concentrations occur 2 to 6 hours after an oral dose of cinacalcet, and are substantially increased if given with food. Clearance from plasma is biphasic, with a terminal half-life of about 30 to 40 hours. Cinacalcet is approximately 93 to 97% bound to plasma proteins. It is rapidly and extensively metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Metabolites are renally excreted, with 80% of the dose recovered in the urine, and 15% in the faeces.

References.
1. Kumar GN, *et al.* Metabolism and disposition of calcimimetic agent cinacalcet HCl in humans and animal models. *Drug Metab Dispos* 2004; **32**: 1491–1500.
2. Padhi D, *et al.* No effect of renal function or dialysis on pharmacokinetics of cinacalcet (Sensipar/Mimpara). *Clin Pharmacokinet* 2005; **44**: 509–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Sensipar; ***Austria***: Mimpara; ***Belg.***: Mimpara; ***Braz.***: Mimpara; ***Canad.***: Sensipa; ***Cz.***: Mimpara; Parareg†; ***Denm.***: Mimpara; ***Fin.***: Mimpara; ***Fr.***: Mimpara; ***Ger.***: Mimpara; ***Gr.***: Mimpara; Sensipar; ***Hong Kong***: Regpara; ***Hung.***: Mimpara; ***Irl.***: Mimpara; ***Israel***: Mimpara; ***Ital.***: Mimpara; Parareg†; ***Jpn***: Regpara; ***Neth.***: Mimpara; ***Norw.***: Mimpara; ***NZ***: Sensipar; ***Pol.***: Mimpara; ***Port.***: Mimpara; ***Rus.***: Mimpara (Мимпара); ***Spain***: Mimpara; ***Swed.***: Mimpara; ***Switz.***: Mimpara; ***Turk.***: Mimpara; ***UK***: Mimpara; ***USA***: Sensipar.

Clodronate

ATC — M05BA02.
ATC Vet — QM05BA02.

Clodronic Acid *(BAN, USAN, rINN)*

Acide Clodronique; Ácido clodrónico; Acidum Clodronicum, Cl_2MBP; Cl_2MDP; Clodrónico, ácido; DkhMDF; Klodronihappo; Klodronsyra; Клодроновая Кислота.

(Dichloromethylene)diphosphonic acid.

$CH_4Cl_2O_6P_2=244.9$

CAS — 10596-23-3.
ATC — M05BA02.
ATC Vet — QM05BA02.
UNII — 0813BZ6866.

Clodronate Disodium *(USAN, rINNM)*

177501; BM-06.011; Clodronas Dinatricum; Clodronate disodique; Clodronate Sodium; Clodronato disódico; Dichloromethane Diphosphonate Disodium; Dichloromethylene Diphosphonate Disodium; Dinatrii Clodronas; Dinatriumklodronaatti; Dinatriumklodronat; Disodium Clodronate; Sodium Clodronate (BANM); Sodyum Klodronat; ZK-00091106; Динатрий Клодронат.

Disodium (dichloromethylene)diphosphonate tetrahydrate.

$CH_2Cl_2Na_2O_6P_2.4H_2O=360.9$

CAS — 22560-50-5.
ATC — M05BA02.
ATC Vet — QM05BA02.
UNII — N030400H8J (clodronate disodium tetrahydrate); Y05R4GCQ1H (anhydrous clodronate disodium).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clodronate Disodium Tetrahydrate). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. A 5% solution in water has a pH of 3.0 to 4.5.

Uses and Administration

Clodronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses. Clodronate is used, generally as the disodium salt, as an adjunct in the treatment of severe hypercalcaemia associated with malignancy. In addition, it is used in the management of osteolytic lesions and bone pain associated with skeletal metastases. Doses are expressed in terms of anhydrous clodronate disodium; 125 mg of clodronate disodium tetrahydrate is equivalent to about 100 mg of anhydrous substance.

Clodronate is given by slow intravenous infusion, diluted in sodium chloride 0.9% or glucose 5%, or orally, as a single daily dose or in 2 divided doses; food should be avoided for at least 1 hour before or 1 hour after an oral dose. Clodronate disodium is available in capsules of 400 mg and standard tablets of 800 mg. Tablets of clodronate disodium 520 mg are also available in some countries, and have a greater bioavailability than the capsules or standard tablets; one such tablet of clodronate disodium 520 mg is considered equivalent to about two capsules each containing clodronate disodium 400 mg or one 800-mg standard tablet (but see Bioavailability, p. 1182.1).

In the management of osteolytic lesions, hypercalcaemia, and bone pain associated with **skeletal metastases** in patients with breast cancer or multiple myeloma, clodronate disodium 1.6 g daily (4 capsules or 2 standard tablets) is given orally, and may be increased if necessary to a maximum of 3.2 g daily. Alternatively a dose of 1.04 g (2 tablets) daily, increased if necessary up to 2.08 g daily, may be given as enhanced bioavailability tablets.

In **hypercalcaemia of malignancy** clodronate disodium is given by intravenous infusion over not less than 2 hours in a dose of 300 mg in 500 mL of infusion solution daily on successive days until normocalcaemia is achieved (usually within 5 days); duration of treatment

should not exceed 7 days. Alternatively, it may be given as a single intravenous infusion of 1.5 g in 500 mL of infusion solution over a period of at least 4 hours. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy may be given orally in similar doses to those used for initial oral treatment of metastases. If hypercalcaemia recurs, the intravenous dose may be repeated.

For details of administration in renal impairment, see below.

General references.

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; 47: 945–82.
2. Kanis JA, McCloskey EV. Clodronate. *Cancer* 1997; 80 (suppl): 1691–5.
3. Brandi ML. Impiego del clodronato nei disordini del metabolismo minerale: stato dell'arte nell'anno 2000. *Minerva Med* 2001; 92: 251–68.
4. Dando TM, Wiseman LR. Clodronate: a review of its use in the prevention of bone metastases and the management of skeletal complications associated with bone metastases in patients with breast cancer. *Drugs Aging* 2004; 21: 949–62.

Administration. In Italy, clodronate is also used *intramuscularly*.[1,2] The usual dose for maintenance therapy of hypercalcaemia is 100 mg daily for 2 to 3 weeks; in the prevention and treatment of postmenopausal osteoporosis, 100 mg is given every 7 to 14 days. However, injection into the gluteal muscle caused local hardening; severe pain at the injection site may limit prolonged use of this route.[1] In Canada, clodronate has been given *subcutaneously* in doses of 1500 mg in 50 to 250 mL of infusion solution over 2 to 3 hours, to treat hypercalcaemia associated with malignancy. The chest and abdomen were the sites most frequently used; pain was the most common adverse effect.[3]

1. Rossini M, *et al.* Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; 24: 125–9.
2. Filipponi P, *et al.* Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; 26: 269–74.
3. Roemer-Bécuwe C, *et al.* Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; 26: 843–8.

Administration in renal impairment. A pharmacokinetic study[1] found that renal clearance of *intravenous* clodronate was highly dependent on renal function. While recommending caution in interpreting these results for patients with malignancy or severe bone disease, the authors recommended the following dose adjustments based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: up to 25% reduction in dose
- CC 12 to 49 mL/minute: 25 to 50% dose reduction
- CC less than 12 mL/minute: 50% dose reduction

Licensed product information recommends similar dose adjustments for intravenous use. In dialysis patients, it is suggested that the daily dose of clodronate disodium 300 mg is infused before haemodialysis sessions, and the dose reduced by 50% on dialysis-free days; duration of treatment should not exceed 5 days. Clodronate is partially removed from the circulation by peritoneal dialysis.

Dose recommendations for *oral* clodronate in renal impairment vary between countries. In the UK the following adjustments are made:

- CC between 10 and 30 mL/minute: 50% dose reduction
- CC below 10 mL/minute: contra-indicated

Alternatively, some other countries such as Canada suggest the following dose adjustments:

- CC 50 to 80 mL/minute: no dose reduction required
- CC 30 to 50 mL/minute: 25% reduction in dose
- CC less than 30 mL/minute: 50% reduction in dose

1. Saha H, *et al.* Pharmacokinetics of clodronate in renal failure. *J Bone Miner Res* 1994; 9: 1953–8.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous clodronate 300 mg daily for 10 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Varenna M, *et al.* Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome: a randomized, double blind, placebo controlled study. *J Rheumatol* 2000; 27: 1477–83.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. Clodronate has been shown to be effective[1–4] in the treatment of malignant hypercalcaemia. A small dose-response study[3] found low-dose clodronate for mild cases to be as effective as high-dose clodronate for moderate to severe cases of tumour-induced hypercalcaemia.

1. O'Rourke NP, *et al.* Effective treatment of malignant hypercalcaemia with a single intravenous infusion of clodronate. *Br J Cancer* 1993; 67: 560–3.
2. Elomaa I, Blomqvist C. Clodronate and other bisphosphonates as supportive therapy in osteolysis due to malignancy. *Acta Oncol* 1995; 34: 629–36.
3. Shah S, *et al.* Is there a dose response relationship for clodronate in the treatment of tumour induced hypercalcaemia? *Br J Cancer* 2002; 86: 1235–7.
4. Roemer-Bécuwe C, *et al.* Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; 26: 843–8.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Clodronate is licensed for such use in many countries. Studies in breast cancer patients with bone metastases found that clodronate reduced the incidence of fractures,[1,2] and delayed the time to onset of new bone events.[2,3] (For mention of the use of clodronate to prevent treatment-related osteoporosis in breast cancer patients see Osteoporosis, below.) A meta-analysis[4] confirmed the benefits of the bisphosphonate in reducing skeletal events and hence morbidity, but not mortality; however, no clear advantage could be shown versus pamidronate or zoledronate, which were also of benefit.

Whether bisphosphonates can prevent the development of new skeletal metastases is unclear. Results of studies using clodronate to reduce skeletal metastases in women with breast cancer have been conflicting,[1,5–7] and one study in women with node-positive disease actually suggested an increase in concomitant visceral metastases.[6] Overall, the studies appeared limited by duration, and further data are needed.[8] In a trial of patients with multiple myeloma,[9] oral clodronate was found to slow the progression of skeletal disease, especially in those patients with less overt disease at diagnosis; the authors suggested starting clodronate early in the course of the disease.

1. Kanis JA, *et al.* Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* 1996; 19: 663–7.
2. Kristensen B, *et al.* Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999; 246: 67–74.
3. Tubiana-Hulin M, *et al.* Essai comparatif randomisé en double aveugle clodronate oral 1600 mg/j versus placebo chez des patientes avec métastases osseuses de cancer du sein: double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. *Bull Cancer* 2001; 88: 701–7.
4. Machado M, *et al.* Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009; 31: 962–79.
5. Diel IJ, *et al.* Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; 339: 357–63.
6. Saarto T, *et al.* Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001; 19: 10–17.
7. Powles T, *et al.* Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002; 20: 3219–24.
8. Hurst M, Noble S. Clodronate: a review of its use in breast cancer. *Drugs Aging* 1999; 15: 143–67.
9. McCloskey EV, *et al.* A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. *Br J Haematol* 1998; 100: 317–25.

Multiple myeloma. For the effect of bisphosphonates, including clodronic acid, on survival in multiple myeloma, see under Bisphosphonates, p. 1174.2.

Osteogenesis imperfecta. Clodronate has been reported to be of benefit in a boy with osteogenesis imperfecta (p. 1167.3) type I. Starting at 13½ years old he was given oral clodronate 400 mg daily for 5 years, and sustained no new low-trauma fractures during this time. Treatment was stopped for 8 months, but bone mineral density remained below normal limits. Clodronate was restarted at 800 mg daily and given with no untoward effects, until the patient was 22 years old, 8 years after initial referral.[1]

1. Ashford RU, *et al.* Oral clodronate as treatment of osteogenesis imperfecta. *Arch Dis Child* 2003; 88: 945.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Clodronate is licensed for this use in some countries. Studies of its use in daily oral doses, or intermittent intravenous infusions,[1] or intramuscular injections (at 7-, 10- or 14-day intervals)[1,2] found increases in bone mineral density at various sites in postmenopausal women with osteoporosis or low bone mass. A large study[3] in postmenopausal women with vertebral osteopenia found that oral clodronate 800 mg daily prevented bone loss in the lumbar spine and femoral trochanter, but not the femoral neck; this dose has been shown to reduce vertebral fracture risk in women with postmenopausal or secondary osteoporosis.[4] The risk of vertebral fractures was also reduced in patients with arthritis receiving corticosteroids, who were given intramuscular clodronate once weekly.[5] Three years of oral clodronate treatment significantly reduced the incidence of spinal osteoporosis in patients with breast cancer who received adjuvant chemotherapy or anti-oestrogens, and this reduction was still evident 7 years after stopping clodronate.[6] Oral clodronate may also be of benefit in reducing bone loss after heart transplantation,[7] but the benefits of intravenous clodronate in a small prospective study in patients receiving parenteral nutrition (who are at high risk of osteoporosis) were uncertain.[8]

1. Filipponi P, *et al.* Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; 26: 269–74.
2. Rossini M, *et al.* Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; 24: 125–9.
3. Vällimäki MJ, *et al.* Prevention of bone loss by clodronate in early postmenopausal women with vertebral osteopenia: a dose-finding study. *Osteoporosis Int* 2002; 13: 937–47.
4. McCloskey E, *et al.* Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004; 19: 728–36.
5. Frediani B, *et al.* Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. *Bone* 2003; 33: 575–81.
6. Saarto T, *et al.* Ten-year follow-up of 3 years of oral adjuvant clodronate therapy shows significant prevention of osteoporosis in early-stage breast cancer. *J Clin Oncol* 2008; 26: 4289–95.
7. Ippoliti G, *et al.* Clodronate treatment of established bone loss in cardiac recipients: a randomized study. *Transplantation* 2003; 75: 330–4.
8. Hadersley KV, *et al.* Effect of cyclical intravenous clodronate therapy on bone mineral density and markers of bone turnover in patients receiving home parenteral nutrition. *Am J Clin Nutr* 2002; 76: 482–8.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. A review[1] of clodronate stated that oral doses of 800 to 1600 mg daily were effective in reducing bone turnover in patients with Paget's disease, and that remission after stopping was longer with the higher dose. Duration of therapy also appears to affect response;[1] longer treatment was associated with a longer time to relapse.[2] Short-term intravenous clodronate (300 mg daily for 5 to 10 days) has also been found to reduce biochemical markers of bone turnover, and sustain remission for up to 1 year.[1,3]

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; 47: 945–82.
2. Khan SA, *et al.* Duration of response with oral clodronate in Paget's disease of bone. *Bone* 1996; 18: 185–90.
3. Broggini M, *et al.* Short courses of intravenous clodronate in the treatment of Paget's disease of bone: a long-term follow-up trial. *Int J Clin Pharmacol Res* 1993; 13: 301–4.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Gastrointestinal symptoms with oral clodronate may be reduced by giving it in divided doses rather than as a single daily dose. Reversible increases in liver enzyme values and serum parathyroid hormone have occurred; transient moderate leucopenia has been reported. Monitoring of hepatic and renal function, white cell counts, and serum calcium and phosphate is advised. Clodronate has precipitated bronchospasm, even in patients with no history of asthma. Transient proteinuria has been reported immediately after intravenous infusion.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including clodronate, see under Bisphosphonates, p. 1175.2.

Effects on the kidneys. For mention of renal failure developing in a patient with slightly raised serum-creatinine concentrations who subsequently received an intravenous infusion of clodronate, see under Bisphosphonates, p. 1176.1.

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including clodronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p. 1176.2).

Effects on the respiratory system. For a report of bronchospasm in an aspirin-sensitive asthmatic, induced by an infusion of clodronate, see p. 1177.1.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. For published reports of cutaneous reactions associated with clodronate, see p. 1177.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clodronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*,[1] or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

1. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* 1993; 4: 432–3.
2. Pedersen-Bjergaard U, Myhre J. Severe hypocalcaemia after treatment with diphosphonate and aminoglycoside. *BMJ* 1991; 302: 295. Correction. *ibid.*; 791.

Pharmacokinetics

Like other bisphosphonates, clodronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is only 1 to 4%, and may differ appreciably between different oral formulations. On absorption or intravenous dosage it is cleared rapidly from the blood with a reported plasma half-life of only about 2 hours, but has a high affinity for bone. Binding to serum plasma proteins is low. Clodronate is not metabolised. Over 70% of an intravenous dose is excreted unchanged in the urine within 24 hours, the remainder being sequestered to bone tissue.

References.

1. Conrad KA, Lee SM. Clodronate kinetics and dynamics. *Clin Pharmacol Ther* 1981; 30: 114–20.
2. Yakatan GJ, *et al.* Clodronate kinetics and bioavailability. *Clin Pharmacol Ther* 1982; 31: 402–10.
3. Ylitalo P, *et al.* Comparison of pharmacokinetics of clodronate after single and repeated doses. *Int J Clin Pharmacol Ther* 1999; 37: 294–300.

Bioavailability. Enhanced bioavailability tablets of clodronate disodium are available in some countries, the licensed dose of which is less than the dose of the standard formulations (see Uses and Administration, p. 1180.3). However, an open, randomised, crossover study in 88 subjects found that a 1040-mg dose of an enhanced tablet formulation provided only 52% of the bioavailable dose of 1600 mg of a standard capsule formulation.[1]

1. Lapham G, *et al.* Bioavailability of two clodronate formulations. *Br J Hosp Med* 1996; 56: 231–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bonefos; ***Austria***: Bonefos; Lodronat; ***Belg.***: Bonefos; ***Braz.***: Bonefos; Ostac†; ***Canad.***: Bonefos; Clasteon; ***China***: Bonefos (固令); De Wei (德维); Di Gai Na (迪盖纳); Ya Kun Yu (雅坤宇); ***Cz.***: Bonefos; Lodronat; ***Denm.***: Bonefos; ***Fin.***: Bonefos; Clodrobon; ***Fr.***: Clastoban; Lytos; ***Ger.***: Bonefos; Clodron beta; Clodron†; Ostac; ***Gr.***: Bonefos; Ostac; ***Hong Kong***: Bonefos; Ostac†; ***Hung.***: Bonefos; ***Indon.***: Bonefos; ***Irl.***: Bonefos; Clasteon; Loron†; ***Israel***: Bonefos; ***Ital.***: Clasteon; Climaclod; Clodeosten; Clodron; Clody; Difosfonal; Moticlod; Niklod; Osteonorm; Osteostab; Soclonat†; ***Malaysia***: Bonefos; ***Mex.***: Bonefos; ***Neth.***: Bonefos; Ostac; ***Norw.***: Bonefos; ***Philipp.***: Bonefos; ***Pol.***: Bonefos; Sindronat; ***Port.***: Bonefos; Ostac; ***Rus.***: Bonefos (Бонефос); Clobir (Клобир); ***S.Afr.***: Bonephos; ***Singapore***: Bonefos; Ostac; ***Spain***: Bonefos; ***Swed.***: Bonefos; Ostac†; ***Switz.***: Bonefos; Ostac†; ***Thai.***: Bonefos; ***Turk.***: Bonefos; Froximun; ***UK***: Bonefos; Clasteon; Loron; ***Ukr.***: ClodronSandoz (КлодронСандоз).

Denosumab *(BAN, USAN, rINN)*

AMG-162; Dénosumab; Denosumabum; Деносумаб.

Immunoglobulin G2, anti-(human RANK ligand) (human monoclonal AMG162 heavy chain), disulfide with human monoclonal AMG162 light chain, dimer.

CAS — 615258-40-7.
ATC — M05BX04.
ATC Vet — QM05BX04.
UNII — 4EQZ6YO2HI.

Uses and Administration

Denosumab is a human monoclonal antibody (p. 2561.1) that specifically targets the receptor activator of nuclear factor-kappa B ligand (RANKL), a mediator of the resorptive phase of bone remodelling. It is used in the treatment of osteoporosis (p. 1168.1) in postmenopausal women or men who are at increased risk of fractures. It is also used in the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and bone loss associated with adjuvant aromatase inhibitor therapy in women with breast cancer at increased risk of fractures. Additionally, denosumab is used for the prevention of skeletal events associated with bone metastases from solid tumours (see Malignant Neoplasms of the Bone, p. 700.3). In the treatment of giant cell tumour of bone, denosumab may be used where the tumour is unresectable or where resection is likely to result in severe morbidity. It is given as a subcutaneous injection into the thigh, abdomen, or upper arm.

For osteoporosis and for bone loss associated with hormone ablation in men with prostate cancer or aromatase inhibitor therapy in women with breast cancer, the recommended dose is denosumab 60 mg once every 6 months.

For prevention of skeletal events associated with bone metastases from solid tumours, denosumab 120 mg is given every 4 weeks.

For giant cell tumour of bone the recommended dose is 120 mg given every 4 weeks with an additional dose of 120 mg given on days 8 and 15 of the first month of therapy.

Calcium and vitamin D supplementation is suggested to prevent hypocalcaemia.

Denosumab is also under investigation for other conditions, including rheumatoid arthritis and multiple myeloma; it is also being studied in the prevention of bone metastases. A few patients with Paget's disease of bone have been treated with denosumab.

References.

1. Stopeck AT, *et al.* Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010; 28: 5132–9.
2. Thomas D, *et al.* Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010; 11: 275–80.
3. Chitre M, *et al.* Denosumab for treatment of postmenopausal osteoporosis. *Am J Health-Syst Pharm* 2011; 68: 1409–18. Correction. *ibid.*: 1676.
4. Scott LJ, Muir VJ. Denosumab: in the prevention of skeletal-related events in patients with bone metastases from solid tumours. *Drugs* 2011; 71: 1059–69.
5. Sutton EE, Riche DM. Denosumab, a RANK ligand inhibitor, for postmenopausal women with osteoporosis. *Ann Pharmacother* 2012; 46: 1000–9.
6. Anonymous. Denosumab for postmenopausal osteoporosis? *Drug Ther Bull* 2012; 50: 6–8.
7. Lipton A, Balakumaran A. Denosumab for the treatment of cancer therapy-induced bone loss and prevention of skeletal-related events in patients with solid tumors. *Expert Rev Clin Pharmacol* 2012; 5: 359–71.
8. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. *Curr Opin Oncol* 2012; 24: 397–403.
9. Smith MR, *et al.* Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012; 379: 39–46.
10. Hageman K, *et al.* The role of denosumab for prevention of skeletal-related complications in multiple myeloma. *Ann Pharmacother* 2013; 47: 1069–74.
11. Ford J, *et al.* Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. *Health Technol Assess* 2013; 17: 1–386. Also available at: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0020/76016/FullReport-hta17290.pdf (accessed 20/08/13)

Adverse Effects and Precautions

The most common adverse effects reported with denosumab include back pain, musculoskeletal pain, hypercholesterolaemia, and cystitis. Other common adverse effects include sciatica, gastrointestinal disturbances such as constipation anaemia, peripheral oedema, asthenia, vertigo, insomnia, pruritus, cardiac disorders such as angina and atrial fibrillation, and other musculoskeletal disorders such as bone pain and myalgia. Skin reactions such as eczema or rash have occurred, and therapy may be stopped if symptoms are severe. Pancreatitis, occasionally fatal, has been reported.

Infections reported during denosumab treatment include upper respiratory-tract infections, cystitis, pharyngitis, and herpes zoster. A higher incidence of serious infections has also been reported, including cellulitis, endocarditis, erysipelas, and infections affecting the abdomen, urinary-tract, and ear. Caution is required in patients also taking immunosuppressive drugs or with an impaired immune system.

Osteonecrosis of the jaw has been reported rarely in patients taking denosumab, as with bisphosphonates (see p. 1176.3). A dental examination should be carried out before starting treatment, and any necessary preventative treatment carried out for those patients with risk factors for osteonecrosis. Good oral hygiene should be maintained during treatment.

Denosumab can cause severe hypocalcaemia and fatalities have occurred. Pre-existing hypocalcaemia should be corrected before treatment begins and calcium and vitamin D supplements should be taken during therapy. Calcium, phosphorus, and magnesium concentrations should be monitored in patients predisposed to hypocalcaemia such as those with severe renal impairment or hypoparathyroidism.

A slightly higher incidence of new malignancies has been reported with denosumab, including breast, reproductive, and gastrointestinal-tract cancers, although a causal link has not been established. In patients with prostate cancer receiving androgen-deprivation therapy, a higher incidence of cataracts and diverticulitis was seen.

Denosumab treatment can suppress bone remodelling and patients should be monitored for adverse outcomes such as delayed fracture healing, atypical fractures, and i osteonecrosis of the jaw.

Pharmacokinetics

Peak plasma concentrations of denosumab occur a media of 10 days after a single subcutaneous dose in a fastin patient. Serum-denosumab concentrations then declin over 3 to 5 months with a mean half-life of about 26 days No accumulation was seen with repeated dosing once ever 6 months. Denosumab is expected to be eliminated vi immunoglobulin clearance pathways, resulting in degrada tion to small peptides and amino acids.

References.

1. Gibiansky L, *et al.* Population pharmacokinetic analysis of denosumab i patients with bone metastases from solid tumours. *Clin Pharmacokinet* 2012; 51: 247–60.
2. Sutjandra L, *et al.* Population pharmacokinetic meta-analysis c denosumab in healthy subjects and postmenopausal women wit osteopenia or osteoporosis. *Clin Pharmacokinet* 2011; 50: 793–807.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Prolia: Xgeva; ***Austria*** Prolia; ***Belg.***: Prolia; Xgeva; ***Canad.***: Prolia; Xgeva; ***Cz.***: Prolia ***Denm.***: Prolia; Xgeva; ***Fr.***: Prolia; Xgeva; ***Ger.***: Prolia: Xgeva ***Gr.***: Prolia; ***Hung.***: Prolia; ***Irl.***: Prolia; Xgeva; ***Israel***: Prolia Xgeva; ***Jpn***: Pralia; Ranmark; ***Neth.***: Prolia; Xgeva; ***Norw.***: Pro lia; Xgeva; ***Pol.***: Prolia; ***Singapore***: Prolia: ***Spain***: Prolia; Xgeva ***Swed.***: Prolia; Xgeva; ***Switz.***: Prolia; ***UK***: Prolia; Xgeva; ***Ukr.*** Prolia (Пролиа); ***USA***: Prolia; Xgeva.

Eldecalcitol *(rINN)*

ED-71; Eldécalcitol; Eldecalcitolum; Эльдекальцитол.

(5*Z*,7*E*)-2β-(3-Hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol.

$C_{30}H_{50}O_5$=490.7
CAS — 104121-92-8.
UNII — I2JP8UE90H.

NOTE. Do not confuse with elocalcitol (p. 2357.3).

Profile

Eldecalcitol is a derivative of vitamin D (p. 2112.3) that is used for the management of osteoporosis (p. 1168.1). The usual oral dose is 750 nanograms daily, although this may be reduced to 500 nanograms in patients unable to tolerate the higher dosage. The main adverse effects are hypercalcaemia and its associated effects such as hypercalciuria.

Reviews.

1. Sanford M, McCormack PL. Eldecalcitol: a review of its use in the treatment of osteoporosis. *Drugs* 2011; 71: 1755–70. Correction. *ibid.* 2390.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Edirol.

Etidronate

ATC — M05BA01.
ATC Vet — QM05BA01.

Etidronic Acid *(BAN, USAN, rINN)*

Acide Étidronique; Ácido etidrónico; Acidum Etidronicum; Etidrónico, ácido; Etidronihappo; Etidronsyra; Этидроновая Кислота.

1-Hydroxyethylidenedi(phosphonic acid).

$C_2H_8O_7P_2$=206.0
CAS — 2809-21-4.
ATC — M05BA01.
ATC Vet — QM05BA01.
UNII — M2F465ROXU.

Etidronate Disodium *(USAN, rINNM)*

Dinatrii etidronas; Dinatriumetidronaatti; Dinatriumetidronat; Dinatrium-etidronát; Disodium Etidronate (BANM); Disodu etydronian; Disodyum Etidronat; EHDP; Etidronas Dinatricum; Etidronat-Dinatrium; Etidronate Disodique; Etidronate disodique; Etidronato disódico; Динатрий Этидронат.

Disodium dihydrogen (1-hydroxyethylidene)diphosphonate.

$C_2H_6Na_2O_7P_2$=250.0
CAS — 7414-83-7.
ATC — M05BA01.
ATC Vet — QM05BA01.
UNII — M16PXG993G.

NOTE. Other etidronic acid sodium salts are designated as etidronate monosodium, etidronate trisodium, and etidronate tetrasodium. The name etidronate sodium is used only in *Martindale* where the salt cannot be identified more precisely.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Etidronate Disodium). A white or yellowish, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.2 to 5.2. Store in airtight containers.

USP 36: (Etidronate Disodium). A white powder that may contain lumps. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. pH of a 1% solution in water is between 4.2 and 5.2.

Uses and Administration

Etidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It inhibits the growth and dissolution of hydroxyapatite crystals in bone and may also directly impair osteoclast activity. It diminishes bone resorption and thus reduces bone turnover.

Etidronate is given in bone disorders in which excessive bone resorption is a problem, such as Paget's disease of bone and osteoporosis. In addition, it may be used for the prevention and treatment of ectopic (heterotopic) ossification. Etidronate may also be given orally after a course of intravenous bisphosphonate in the management of hypercalcaemia of malignancy. A chelate of etidronate with radioactive technetium-99m (p. 2228.1) is used diagnostically as a bone scanning agent and a similar compound with rhenium-186 for the palliation of bone metastases in prostate cancer (see below).

Etidronate is given orally as the disodium salt, usually as a single daily dose. Food should be avoided for 2 hours before and after oral doses. Etidronate disodium has also been given by slow intravenous infusion.

In the treatment of **Paget's disease**, etidronate disodium is given orally in a usual initial dose of 5 mg/kg daily for not more than 6 months. Doses above 10 mg/kg daily should be reserved for severe disease and should not be given for more than 3 months at a time. The maximum dose is 20 mg/kg daily. The response to etidronate may be slow in onset and may continue for several months after stopping therapy. Therefore, further treatment should only be given after a drug-free interval of at least 3 months and after evidence of relapse; it should not be given for longer than the initial treatment.

For the treatment of **osteoporosis**, the prevention of bone loss in postmenopausal women, and the prevention and treatment of corticosteroid-induced osteoporosis, etidronate is given in an intermittent or cyclical regimen with a calcium salt; oral etidronate disodium 400 mg is given daily for 14 days followed by the equivalent of 500 mg of elemental calcium orally for 76 days. Treatment has continued for 3 years in most patients; a small number of patients have been successfully treated for up to 7 years. The optimum duration of treatment has not been established.

For the prevention and treatment of **ectopic ossification** complicating hip replacement etidronate disodium has been given orally in a dose of 20 mg/kg daily for 1 month before and 3 months after the operation. For ectopic ossification due to spinal cord injury it has been given in a dose of 20 mg/kg daily for 2 weeks followed by 10 mg/kg daily for 10 weeks.

Etidronate may be given in the management of **hypercalcaemia of malignancy**, to maintain serum-calcium concentrations at an acceptable level after initial treatment with an intravenous bisphosphonate. Etidronate disodium 20 mg/kg daily is given orally for 30 days, starting on the day after the last intravenous bisphosphonate dose. If effective, etidronate treatment may be extended to a maximum of 90 days.

For details of administration in renal impairment, see below.

Administration in renal impairment. The *BNF* has recommended that the oral dose of etidronate should be reduced in patients with mild renal impairment, and that its use should be avoided when impairment is more severe.

Ectopic ossification. Bisphosphonates that inhibit bone mineralisation such as etidronate have been used to prevent ectopic ossification (p. 103.2). Some studies, using higher and more prolonged oral doses (20 mg/kg daily for 6 months) than are generally recommended for treatment after spinal cord injury, have suggested that this may improve effectiveness.[1,2] Etidronate has also been used to treat calciphylaxis and vascular and soft-tissue calcification associated with haemodialysis.[3-5]

1. Banovac K, *et al.* Treatment of heterotopic ossification after spinal cord injury. *J Spinal Cord Med* 1997; 20: 60–65.
2. Banovac K. The effect of etidronate on late development of heterotopic ossification after spinal cord injury. *J Spinal Cord Med* 2000; 23: 40–4.
3. Hashiba H, *et al.* Inhibition of the progression of aortic calcification by etidronate treatment in hemodialysis patients: long-term effects. *Ther Apher Dial* 2006; 10: 59–64.
4. Shiraishi N, *et al.* Successful treatment of a patient with severe calcific uremic arteriolopathy (calciphylaxis) by etidronate disodium. *Am J Kidney Dis* 2006; 48: 151–4.
5. Mori H, *et al.* Etidronate for the treatment of progressive tumoral calcinosis in hemodialysis patients. *Intern Med* 2007; 46: 1485–6.

Hypercalcaemia. Bisphosphonates (including etidronate although other bisphosphonates may be more suitable) are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated.

There are reports of response[1-3] to oral etidronate 5 mg/kg twice daily in the treatment of hypercalcaemia associated with subcutaneous fat necrosis of the newborn refractory to standard treatment.

1. Rice AM, Rivkees SA. Etidronate therapy for hypercalcemia in subcutaneous fat necrosis of the newborn. *J Pediatr* 1999; 134: 349–51.
2. Wiadrowski TP, Marshman G. Subcutaneous fat necrosis of the newborn following hypothermia and complicated by pain and hypercalcaemia. *Australas J Dermatol* 2001; 42: 207–10.
3. Trullemans B, *et al.* Etidronate per os dans le cadre d'une hypercalcémie secondaire à une cytostéatonécrose compliquée de néphrocalcinose. *Arch Pediatr* 2007; 14: 170–2.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3). Etidronate, labelled with rhenium-186 or its isotope rhenium-188, is used for the palliation of painful bone metastases of prostate,[1,2] breast,[3,4] lung,[4,5] and various other cancers.[4]

1. Han SH, *et al.* The Placorhen study: a double-blind, placebo-controlled, randomized radionuclide study with ^{186}Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. *J Nucl Med* 2002; 43: 1150–6.
2. Liepe K, *et al.* Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases. *Br J Cancer* 2003; 89: 625–9.
3. Sciuto R, *et al.* Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. *Breast Cancer Res Treat* 2001; 66: 101–9.
4. Li S, *et al.* Rhenium-188 HEDP to treat painful bone metastases. *Clin Nucl Med* 2001; 26: 919–22.
5. Zhang H, *et al.* Rhenium-188-HEDP therapy for the palliation of pain due to osseous metastases in lung cancer patients. *Cancer Biother Radiopharm* 2003; 18: 719–26.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including etidronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p. 1168.1). Etidronate is used in a cyclical regimen for both the treatment and prevention of **postmenopausal** osteoporosis. It increases bone mineral density (BMD), largely in the lumbar spine and femoral neck, and reduces the risk of vertebral fractures,[1,2] but not non-vertebral fractures.[2] Additive effects on BMD have been found when etidronate was used with oestrogen.[1] Etidronate also prevents bone loss and maintains or increases BMD in **corticosteroid-induced** osteoporosis,[1,3] and has shown some benefit in reducing bone loss after organ transplantation.[1] In an uncontrolled study[4] in men with idiopathic vertebral osteoporosis, cyclical etidronate increased BMD at the lumbar spine.

1. Hanley DA, *et al.* Etidronate therapy in the treatment and prevention of osteoporosis. *J Clin Densitom* 2000; 3: 79–95.
2. Wells GA, *et al.* Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
3. Adachi JD, *et al.* A pooled data analysis on the use of intermittent cyclical etidronate therapy for the prevention and treatment of corticosteroid induced bone loss. *J Rheumatol* 2000; 27: 2424–31.
4. Anderson FH, *et al.* Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures. *Age Ageing* 1997; 26: 359–65.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Initial experience was with etidronate, but bisphosphonates that have less effect on bone mineralisation may be preferred. In studies, alendronate[1] and risedronate[2] were found to be more effective than etidronate.

1. Siris E, *et al.* Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab* 1996; 81: 961–7.
2. Miller PD, *et al.* A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; 106: 513–20.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Unlike the newer bisphosphonates etidronate produces marked impairment of bone mineralisation at high therapeutic doses. An increase in bone pain may occur in patients with Paget's disease. Impairment of bone mineralisation may result in osteomalacia, and fractures have been reported. If a fracture occurs etidronate should be stopped until healing is complete. Hyperphosphataemia may occur, usually at high doses, but generally resolves 2 to 4 weeks after the end of therapy. There have been reports of paraesthesias, peripheral neuropathy, and confusion. Burning of the tongue, alopecia, erythema multiforme, and exacerbation of asthma have occurred rarely. Transient loss or alteration of taste has been reported mainly during and after intravenous infusion.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, including etidronate, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the blood. For a report of pancytopenia caused by etidronate therapy, see Effects on the Skin, below.

Effects on the ears. Ototoxicity, manifest as tinnitus and hearing loss, has been reported[1] in 2 patients given etidronate for osteoporosis; both patients had pre-existing otosclerosis and the authors recommended that those with ear pathology be monitored audiometrically when given bisphosphonates.

1. Yeşil S, *et al.* Further hearing loss during osteoporosis treatment with etidronate. *Postgrad Med J* 1998; 74: 363–4.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including etidronate, see under Bisphosphonates, p. 1175.2.

Effects on the gastrointestinal tract. Oral etidronate was not associated with an increased incidence of upper gastrointestinal problems in a retrospective cohort study.[1] There was also no evidence of an increased incidence of gastrointestinal effects when given with NSAIDs or corticosteroids. Similarly, another large cohort study found no increased risk of peptic ulcer disease associated with the use of cyclical etidronate.[2] However, oesophageal ulceration has been reported with daily etidronate;[3,4] in one case possibly associated with incorrect use,[3] and in another, complicated by prior use of diclofenac, and a history of gastro-oesophageal reflux disease.[4]

1. van Staa T, *et al.* Upper gastrointestinal adverse events and cyclical etidronate. *Am J Med* 1997; 103: 462–7.
2. Burger H, *et al.* Cyclical etidronate use is not associated with symptoms of peptic ulcer disease. *Eur J Clin Pharmacol* 2000; 56: 319–22.
3. Macedo G, *et al.* Ulcerative esophagitis caused by etidronate. *Gastrointest Endosc* 2001; 53: 250–1.
4. Maroy B. Ulcère géant de l'œsophage probablement dû à la prise d'étidronate. *Gastroenterol Clin Biol* 2001; 25: 917–18.

Effects on the kidneys. Bisphosphonates are excreted by the kidneys, thus caution is advised in patients with renal impairment. When given by intravenous infusion for the treatment of hypercalcaemia of malignancy they have been reported to affect renal function adversely; hypercalcaemia or malignancy may also have contributed. For reports of renal failure associated with etidronate see under Bisphosphonates, p. 1176.1.

Effects on the musculoskeletal system. Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

Effects on mental state. Sensory hallucinations and confusion were reported in an elderly woman given daily etidronate for a week. Symptoms resolved on stopping the drug and recurred on rechallenge.[1] Mood disturbances, lack of concentration, and memory impairment were also reported in 3 patients receiving longer-term cyclical treatment; symptoms again diminished on stopping etidronate and reappeared after rechallenge.[2]

1. Burnet SP, Petrie JP. Wake up and smell the roses'—a drug reaction to etidronate. *Aust N Z J Med* 1999; 29: 93.
2. Wolffenbuttel BHR, van der Klauw MM. Psychische bijwerkingen van behandeling met bisfosfonaten. *Ned Tijdschr Geneeskd* 2003; 147: 35–7.

Effects on the respiratory system. For a report of bronchospasm induced by etidronate in an aspirin-sensitive asthmatic, see p. 1177.1. For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, below.

Effects on the skin. A 47-year old woman with a history of auto-immune rheumatic disease developed toxic epidermal necrolysis, pancytopenia, and acute respiratory distress syndrome 7 days after starting etidronate for osteoporosis; she died of cardiorespiratory failure, secondary to the acute respiratory distress syndrome, despite aggressive supportive measures.[1]

1. Coakley G, Isenberg DA. Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. *Br J Rheumatol* 1995; 34: 798.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare (see p. 1177.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies etidronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Anti-inflammatory drugs. For a lack of apparent interaction between cyclical etidronate and corticosteroids or NSAIDs see under Effects on the Gastrointestinal Tract, p. 1183.3.

Pharmacokinetics

After oral doses of etidronate, absorption is variable and appears to be dose dependent. At usual doses about 1 to 6% of a dose is absorbed. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. Etidronate is rapidly cleared from the blood and has been reported to have a plasma half-life of 1 to 6 hours. It is not metabolised. About 50% is excreted in the urine within 24 hours, the remainder being sequestered to bone and slowly eliminated. The half-life of etidronate in bone exceeds 90 days. Unabsorbed etidronate appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Difosfen; *Austral.*: Didronel; *Austria*: Didronel†; *Belg.*: Osteodidronel; *Canad.*: Didronel†; *China*: Bang Te Lin (邦特林); Gende (根德); Luodi (洛迪); Yilin (依麟); *Denm.*: Didronate†; Didronel; *Fin.*: Didronate†; *Fr.*: Didronel; *Ger.*: Didronel†; Diphos†; Etidron†; *Gr.*: Anfozan; Biotredine; Dralen; Eopon; Etidron; Etiplus; Feminoflex; Maxibral; Oflodin; Osfo; Ostedron; Osteodrug; Osteoton; Ostogene; Ostopor; Somaflex; Sterodome; Sviroxit; Tilferan; *India*: Disonate; Dronate-OS†; Etifem; *Irl.*: Didronel†; *Israel*: Didronel; *Ital.*: Etidron; *Jpn*: Didronel; *Neth.*: Didronel†; *Norw.*: Didronate; *NZ*: Didronel; Etidrate†; *Pol.*: Ostedron†; *Rus.*: Xydifon (Ксидифон); *Singapore*: Difosfen; *Spain*: Difosfen†; Osteum; *Swed.*: Didronate†; *Switz.*: Didronel†; *Thai.*: Difosfen; *Turk.*: Didronat; *UK*: Didronel; *USA*: Didronel.

Multi-ingredient Preparations. *Arg.*: Emoform Total; Squam; Squam; *Austral.*: Didrocal; *Canad.*: Didrocal; Etidrocal; Gen-Eti-Cal†; Novo-Etidronatecal; *Denm.*: Didronate Calcium†; *Fin.*: Didronate + Calcium†; *Ger.*: Didronel Kit; *Irl.*: Didronel PMO†; *Neth.*: Didrokit; *Norw.*: Didronate + Calsium†; *Swed.*: Didronate + Calcium; *UK*: Didronel PMO†; Tiloetca Combi.

Pharmacopoeial Preparations
BP 2014: Etidronate Tablets;
USP 36: Etidronate Disodium Tablets.

Gallium Nitrate *(USAN)*

Gallo, nitrato de; NSC-15200; WR-135675.
$Ga(NO_3)_3.9H_2O$=417.9
CAS — 13494-90-1 (anhydrous gallium nitrate); 135886-70-3 (gallium nitrate nonahydrate).
UNII — VRA0C6810N (gallium nitrate); Y2V2R4W9TQ (anhydrous gallium nitrate).

Uses and Administration

Gallium nitrate is an inorganic metallic salt with hypocalcaemic properties. It acts to decrease bone resorption by osteoclasts, with a lesser and probably indirect increase in bone formation, and a consequent decline in serum calcium.

Gallium nitrate is used in the treatment of hypercalcaemia associated with malignant neoplasms. It has been investigated in other disorders associated with abnormally enhanced bone turnover, such as Paget's disease of bone, and is under investigation in refractory non-Hodgkin's lymphoma. For the treatment of hypercalcaemia of malignancy doses of 100 to 200 mg/m² may be given daily for up to 5 days, diluted in 1 litre of sodium chloride 0.9% or glucose 5% and infused intravenously over 24 hours. Adequate hydration before and during treatment is essential: a urinary output of at least 2 litres daily should be maintained, and renal function should be regularly monitored.

Hypercalcaemia. Gallium nitrate is used in the treatment of hypercalcaemia of malignancy (p. 1167.2). It appears to be effective in patients with solid tumours and increased levels of parathyroid-related protein.[1,2]

1. Chitambar CR. Gallium nitrate revisited. *Semin Oncol* 2003; **30** (suppl): 1–4.
2. Leyland-Jones B. Treatment of cancer-related hypercalcemia: the role of gallium nitrate. *Semin Oncol* 2003; **30** (suppl): 13–19.

Paget's disease of bone. Beneficial results[1] were reported when gallium nitrate was given subcutaneously in doses of 250 or 500 micrograms/kg daily for 14 days to patients with advanced Paget's disease of bone (p. 1169.3). In this pilot multicentre study 14 days of gallium nitrate injections were followed by 4 weeks off medication and the cycle repeated once.

1. Bockman RS, *et al.* A multicenter trial of low dose gallium nitrate in patients with advanced Paget's disease of bone. *J Clin Endocrinol Metab* 1995; **80**: 595–602.

Adverse Effects, Treatment, and Precautions

Gallium nitrate may produce serious nephrotoxicity, especially when given as a brief intravenous infusion; continuous infusion, with adequate hydration, may reduce the incidence of renal damage. Serum creatinine should be monitored during therapy and treatment stopped if it exceeds 25 mg/litre. Gallium nitrate should be given with great care and in reduced doses, if at all, to patients with existing renal impairment.

Gastrointestinal disturbances, rashes, metallic taste, visual and auditory disturbances, anaemia, hypophosphataemia, and hypocalcaemia have also been reported.

Effects on the nervous system. Although it has been suggested, given the chemical similarity of gallium to aluminium, that repeated doses, particularly in the presence of renal impairment, might lead to severe neurotoxicity,[1] studies in *rats* do not provide any evidence of central neurological abnormalities.[2]

1. Altmann P, Cunningham J. Hazards of gallium for the treatment of Paget's disease of bone. *Lancet* 1990; **335**: 477.
2. Matkovic V, *et al.* Hazards of gallium for Paget's disease of bone. *Lancet* 1990; **335**: 1099. Correction. *ibid.*; 1352.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ganite.

Ibandronate

ATC — M05BA06.
ATC Vet — QM05BA06.

Ibandronic Acid *(BAN, rINN)*

Acide Ibandronique; Ácido ibandrónico; Acidum Ibandronicum; BM-21.0955; Ibandrónico, ácido; Ibandronik Asit; Ибандроновая Кислота.
(1-Hydroxy-3-(methylpentylamino)propylidene)diphosphonic acid.
$C_9H_{23}NO_7P_2$=319.2
CAS — 114084-78-5.
ATC — M05BA06.
ATC Vet — QM05BA06.
UNII — UMD7G2653W.

Ibandronate Sodium *(USAN)*

Ibandronate de Sodium; Ibandronato sódico; Natrii Ibandronas; Natriumibandronaatti; Natriumibandronat; Sodium Ibandronate (rINNM); Sodium Ibandronate (BANM); Натрий Ибандронат.
$C_9H_{22}NNaO_7P_2.H_2O$=359.2
CAS — 138926-19-9.
ATC — M05BA06.
ATC Vet — QM05BA06.
UNII — J12U072QL0.

Uses and Administration

Ibandronate is an aminobisphosphonate (p. 1173.3) that is a potent inhibitor of bone resorption. It is used as the sodium salt in hypercalcaemia of malignancy, for the prevention of fracture and bone complications in patients with breast cancer and bone metastases, and for the treatment and prevention of postmenopausal osteoporosis.

Ibandronate sodium is given by intravenous infusion or orally, the dose being expressed in terms of ibandronic acid; ibandronate sodium 1.13 mg is equivalent to about 1 mg of ibandronic acid. Specific instructions for oral use (see Precautions in Alendronate, p. 1172.3) should be followed to minimise adverse effects and permit adequate absorption.

For **hypercalcaemia of malignancy**, a single intravenous dose of the equivalent of 2 to 4 mg ibandronic acid is given, up to a maximum of 6 mg; it is diluted in 500 mL of sodium chloride 0.9% or glucose 5%, and infused over 2 hours.

For the prevention of skeletal events in patients with breast cancer and **bone metastases**, the equivalent of 6 mg ibandronic acid is given intravenously, diluted in 100 mL of sodium chloride 0.9% or glucose 5%, and infused over at least 15 minutes. The dose is repeated every 3 to 4 weeks. Alternatively, ibandronic acid 50 mg daily may be given orally.

For the prevention and treatment of postmenopausal **osteoporosis**, ibandronate is given orally in a usual dose equivalent to 150 mg of ibandronic acid once monthly on the same date each month; alternatively, 2.5 mg daily may be given. If the once-monthly dose is missed, and the next scheduled dose is more than 7 days away, the dose should be taken the next morning, and the patient should then return to the original schedule. However, if the next dose is less than 7 days away, then the patient should wait until that next scheduled dose; 2 tablets must not be taken within the same week. Alternatively, treatment may be given intravenously, in a dose equivalent to 3 mg of ibandronic acid once every 3 months; the injection is given over 15 to 30 seconds. If the dose is missed, the injection should be given as soon as possible; the next injection should then be rescheduled 3 months from this injection, as it should not be given more frequently than once every 3 months.

For details of doses in renal impairment, see below.

General references.

1. Dooley M, Balfour JA. Ibandronate. *Drugs* 1999; **57**: 101–108.
2. Barrett J, *et al.* Ibandronate: a clinical pharmacological and pharmacokinetic update. *J Clin Pharmacol* 2004; **44**: 951–65.
3. Anonymous. Ibandronate (Boniva): a new oral bisphosphonate. *Med Lett Drugs Ther* 2005; **47**: 35.
4. Guay DR. Ibandronate, an experimental intravenous bisphosphonate for osteoporosis, bone metastases, and hypercalcemia of malignancy. *Pharmacotherapy* 2006; **26**: 655–73.
5. Zaidi M, *et al.* Progression of efficacy with ibandronate: a paradigm for the development of new bisphosphonates. *Ann N Y Acad Sci* 2007; **1117**: 273–82.
6. Reginster JY, *et al.* Ibandronate in profile: drug characteristics and clinical efficacy. *Expert Opin Drug Metab Toxicol* 2008; **4**: 941–51.

Administration in renal impairment. UK and US licensed product information for ibandronate states that the dose should be adjusted on the basis of creatinine clearance (CC).

When used for the prevention of skeletal events in patients with breast cancer and **bone metastases**, the following *oral* doses are recommended:

- CC equal to or greater than 50 mL/minute: no adjustment necessary
- CC less than 50 mL/minute but equal to or greater than 30 mL/minute: 50 mg every other day
- CC below 30 mL/minute: 50 mg once weekly

Since a 15-minute infusion time has not been studied in cancer patients with a CC less than 50 mL/minute, the following *intravenous* doses are recommended, to be given every 3 to 4 weeks in a solution of sodium chloride 0.9% or glucose 5%:

- CC equal to or greater than 50 mL/minute: no adjustment necessary
- CC less than 50 mL/minute, but equal to or greater than 30 mL/minute: 4 mg in 500 mL of infusion solution, infused over 1 hour
- CC less than 30 mL/minute: 2 mg in 500 mL of infusion solution, infused over 1 hour

In patients with **osteoporosis**, the following recommendations are given, for *oral* or *intravenous* use:

- mild or moderate renal impairment (CC equal to or greater than 30 mL/minute): no adjustment necessary
- CC below 30 mL/minute: not recommended

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. In a dose-response study,[1] 2 mg of ibandronate was found to be significantly less effective than 4 or 6 mg in correcting hypercalcaemia, and response was better in those patients with breast cancer or haematological tumours. In comparison to pamidronate,[2] ibandronate was reported to be more effective in those patients with higher initial baseline serum calcium; duration of response was also longer with ibandronate. In a series of case reports, intravenous ibandronate rapidly corrected hypercalcaemia and restored renal function in multiple myeloma patients. The authors suggested that, although unlicensed for this use, ibandronate should be considered in this patient population.[3]

1. Ralston SH, *et al.* Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. *Br J Cancer* 1997; **75**: 295–300.
2. Pecherstorfer M, *et al.* Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer* 2003; **11**: 539–47.
3. Henrich D, *et al.* Ibandronate for the treatment of hypercalcemia or nephrocalcinosis in patients with multiple myeloma and acute renal failure: case reports. *Acta Haematol (Basel)* 2006; **116**: 165–72.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Ibandronate is licensed for such use in many countries. In patients with bone metastases from breast cancer, both oral[1] and intravenous[2] ibandronate reduced the skeletal morbidity period rate (the number of 12-week periods with new bone complications). A pilot study[3] in

18 patients with skeletal metastases from various tumours, and with bone pain insufficiently controlled with opioid analgesics, found short-term intensive intravenous ibandronate (4 mg for 4 consecutive days) to significantly reduce bone pain scores; this analgesic effect was obtained within 7 days, and sustained for a further 5 weeks. A review[4] concluded that once-monthly intravenous dosing could aid compliance, since it can be given simultaneously with cancer therapy; the absence of any apparent renal toxicity associated with ibandronate was a further advantage in its use in cancer patients.

Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Tripathy D, *et al.* Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* 2004; **15**: 743–50.
2. Body J-J, *et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003; **14**: 1399–1405.
3. Mancini I, *et al.* Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. *J Clin Oncol* 2004; **22**: 3587–92.
4. McCormack PL, Plosker GL. Ibandronic acid: a review of its use in the treatment of bone metastases of breast cancer. *Drugs* 2006; **66**: 711–28.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). In the treatment of **postmenopausal** osteoporosis, *oral* ibandronate in intermittent regimens of 20 mg every alternate day,[1] or 20 mg weekly[2] has been found to have equivalent effects on bone mineral density (BMD) to 2.5 mg daily. Intermittent oral ibandronate (20 mg every alternate day for 12 doses every 3 months) was also as effective as the lower daily dose in reducing the incidence of osteoporotic fractures in postmenopausal women.[3] In the prevention of postmenopausal osteoporosis, both 2.5 mg daily[4] and 20 mg weekly[5] prevented bone loss at the spine and hip. A large study comparing three different monthly regimens with the 2.5 mg daily regimen found them to be of similar efficacy in terms of improvement in lumbar BMD after 1 year; 150 mg given once monthly was considered to be superior to the low-dose daily regimen.[6] A review[7] concluded that this unique once-monthly regime could benefit patients by improving compliance.

Intravenous ibandronate 2 mg given every 3 months has also proven effective in increasing BMD in the treatment[8] and prevention[9] of postmenopausal osteoporosis. A large, randomised, double-blind study compared 2 intravenous regimens (2 mg every 2 months and 3 mg every 3 months) with oral ibandronate 2.5 mg daily in postmenopausal women with osteoporosis. After 1 year, both intravenous regimens increased lumbar BMD scores significantly more than the oral regimen. Similar results were obtained for proximal femoral BMD scores, except that for femoral neck BMD, the 2-monthly regimen and daily oral regimen were not significantly different.[10] After 2 years, these results were reported to have been maintained.[11] In **corticosteroid-induced** osteoporosis, intravenous ibandronate 2 mg every 3 months was better than daily oral alfacalcidol at reducing vertebral fractures.[12,13] Intravenous ibandronate has also shown to be of benefit in reducing bone loss after kidney **transplantation.**[14] A pilot study[15] of intermittent ibandronate given intravenously to men with severe osteoporosis significantly increased BMD at the lumbar spine, trochanter, and femoral neck.

1. Riis BJ, *et al.* Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. *J Bone Miner Res* 2001; **16**: 1871–8.
2. Cooper C, *et al.* Efficacy and safety of oral weekly ibandronate in the treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88**: 4609–15.
3. Chesnut CH, *et al.* Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004; **19**: 1241–9.
4. McClung MR, *et al.* Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res* 2004; **19**: 11–18.
5. Tankó LB, *et al.* Oral weekly ibandronate prevents bone loss in postmenopausal women. *J Intern Med* 2003; **254**: 159–67.
6. Miller PD, *et al.* Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* 2005; **20**: 1315–22.
7. Chesnut CH. Treating osteoporosis with bisphosphonates and addressing adherence: a review of oral ibandronate. *Drugs* 2006; **66**: 1351–9.
8. Adami S, *et al.* Efficacy and safety of ibandronate given by intravenous injection once every 3 months. *Bone* 2004; **34**: 881–9.
9. Stakkestad JA, *et al.* Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. *Ann Rheum Dis* 2003; **62**: 969–75.
10. Delmas PD, *et al.* Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006; **54**: 1838–46.
11. Croom KF, Scott LJ. Intravenous ibandronate: in the treatment of osteoporosis. *Drugs* 2006; **66**: 1593–1601.
12. Ringe JD, *et al.* Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. *Osteoporosis Int* 2003; **14**: 801–7.
13. Ringe JD, *et al.* Three-month ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis. *Rheumatology (Oxford)* 2003; **42**: 743–9.
14. Grotz W, *et al.* Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001; **12**: 1530–7.
15. Lamy O, *et al.* Intravenous ibandronate in men with osteoporosis: an open pilot study over 2 years. *J Endocrinol Invest* 2003; **26**: 728–32.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Gastrointestinal symptoms such as abdominal pain, dyspepsia, and nausea are the most frequent adverse effects with oral ibandronate. Severe oesophageal reactions such as oesophagitis, and ulceration have occurred; patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn. Gastric ulceration has been reported. To minimise the risk of oesophageal reactions, precautions similar to those for alendronate (see p. 1172.3) should be observed. Anaemia and bronchospasm have occurred rarely, as has taste disturbance, paraesthesia, and uraemia. Serum calcium, magnesium, and phosphate should be monitored. Hypocalcaemia should be corrected before starting ibandronate therapy; adequate intake of calcium and vitamin D is important. Transient fever after parenteral use is common. Flu-like symptoms have been reported after both parenteral and intermittent oral use, typically after the first dose.

Effects on the musculoskeletal system. Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, including ibandronate, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibandronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Like other bisphosphonates, ibandronate is poorly absorbed after oral doses; absolute bioavailability is less than 1%. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is reduced by about 90% when given with food, by about 30% when given half an hour before food, and by about 75% when given 2 hours after food. About half of the absorbed portion is sequestered to bone; the remainder is excreted in urine. Plasma protein binding is about 87%. Bisphosphonates do not appear to be metabolised, and the unabsorbed fraction of ibandronate is excreted unchanged in the faeces.

References.
1. Bergner R, *et al.* Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. *J Clin Pharmacol* 2007; **47**: 942–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adromux; Bandrobon; Bantuc; Bonviva; Brexell Plus; Deltrox; Elasterin; Femorel; Ibanleg; Idena; Mesel; Modifical; Silidral Uno; ***Austral.***: Bondronat; ***Austria***: Bondronat; Bonviva; ***Belg.***: Bondronat; Bonviva; ***Braz.***: Bonviva; ***Chile***: Bondronat; Bonviva; Darmas; Dronaval; Ibadrox; Ibames; Idena; Recaxin; ***China***: Ai Ben (艾本); Bondronat (邦罗力); Jia Nuo Shun (佳诺顺); ***Cz.***: Baxogar; Bondenza†; Bondronat; Bonviva; Etanorden; Gerousia; Iasibon; Mirdezel; Ossica; Quodixor; ***Denm.***: Bondronat; Bonviva; Etanorden; Iasibon; ***Fin.***: Bondronat; Bonviva; Clastec; Ibamyl; ***Fr.***: Bondronat; Bonviva; ***Ger.***: Bondronat; Bonviva; ***Gr.***: Bondronat; Bonviva; ***Hong Kong***: Bondronat; Bonviva; ***Hung.***: Bondronat; Bonviva; Ossica; ***India***: Bandrone; Bondronat; Bonviva; Idrofos; ***Indon.***: Bondronat; Bonviva; ***Irl.***: Bondenza†; Bondronat; Bonefurbit; Bonviva; Iasibon; Kefort; Osbonelle; ***Israel***: Bonat; ***Ital.***: Bondronat; Bonviva; Etanorden; Licobondrat; ***Jpn***: Bonviva; ***Malaysia***: Bonviva; ***Mex.***: Bondronat†; Bonviva; ***Neth.***: Baxogar; Bondenza†; Bondronat; Bonefurbit; Bonviva; Destara†; Etanorden; Iasibon; Ibagenit; IbandroMylan; Ikametin; Licobondrat; Osbonelle; Phacebonate; Quodixor; Ribobandron; ***Norw.***: Bondronat; Bonviva; ***Philipp.***: Bondronat; Bonviva; ***Pol.***: Bondenza†; Bondronat; Bonviva; Iasibon; Ossica; ***Port.***: Bondenza†; Bondronat; Bonviva; Destara†; ***Rus.***: Bondronat (Бондронат); Bonviva (Бонвива); ***S.Afr.***: Bondronat; ***Singapore***: Bondronat; Bonviva; ***Spain***: Abrion; Bondenza†; Bondronat; Bonviva; ***Swed.***: Bondronat; Bonviva; ***Switz.***: Bondronat; Bonviva; ***Thai.***: Bondronat†; Bonviva; ***Turk.***: Bondronat; Bonviva; Osiban; ***UK***: Bondronat; Bonviva; ***Ukr.***: Bondronat (Бондронат); Bonviva (Бонвива); ***USA***: Boniva.

Multi-ingredient Preparations. ***Arg.***: Femorel Max; Modifical Duo.

Incadronate

Incadronic Acid *(rINN)*

Acide Incadronique; Ácido Incadrónico; Acidum Incadronicum; Cimadronic Acid; Incadrónico, ácido; YM-175; Инкадроновая Кислота.

[(Cycloheptylamino)methylene]diphosphonic acid.

$C_8H_{19}NO_6P_2$=287.2

CAS — 124351-85-5.

UNII — G5C4M8847E.

Incadronate Disodium

Disodium Incadronate (rINNM); Incadronas Dinatricum; Incadronate Disodique; Incadronato disódico; Динатрий Инкадронат.

Disodium [(cycloheptylamino)methylene]diphosphonate.

$C_8H_{17}NNa_2O_6P_2$=331.2

CAS — 138330-18-4.

Profile

Incadronate is an aminobisphosphonate (p. 1173.3) that is a potent inhibitor of bone resorption. It is given by intravenous infusion as incadronate disodium for hypercalcaemia of malignancy in a dose of 10 mg over 2 to 4 hours; if necessary this dose may be repeated at intervals of no less than 1 week. Hypocalcaemia and hypotension may occur. Incadronate is under investigation for the treatment of bone metastases in patients with breast cancer.

References.
1. Usui T, *et al.* Pharmacokinetics of incadronate, a new bisphosphonate, in healthy volunteers and patients with malignancy-associated hypercalcemia. *Int J Clin Pharmacol Ther* 1997; **35**: 239–44.
2. Matsumoto T, *et al.* Comparative study of incadronate and elcatonin in patients with malignancy-associated hypercalcaemia. *J Int Med Res* 2002; **30**: 230–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Yin Pu (茵福); ***Jpn***: Bisphonal†; ***Philipp.***: Bisphonal; ***Thai.***: Bisphonal.

Ipriflavone *(rINN)*

FL-113; Ipriflavona; Ipriflavonum; Иприфлавон.

7-Isopropoxyisoflavone.

$C_{18}H_{16}O_3$=280.3

CAS — 35212-22-7.

ATC — M05BX01.

ATC Vet — QM05BX01.

UNII — 80BJ7WN25Z.

Profile

Ipriflavone is a synthetic isoflavonoid that inhibits resorption of bone and is available in some countries for the treatment of osteoporosis (p. 1168.1). It is given orally in a dose of 200 mg three times daily.

Osteoporosis. Despite an earlier favourable report,[1] a prospective randomised controlled study in postmenopausal women with low bone mass failed to show prevention of bone loss or improvements in markers of bone metabolism with ipriflavone.[2] There was also a significant incidence of lymphopenia with the drug.

1. Agnusdei D, *et al.* Effects of Ipriflavone on bone mass and bone remodeling in patients with established postmenopausal osteoporosis. *Curr Ther Res* 1992; **51**: 82–91.
2. Alexandersen P, *et al.* Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001; **285**: 1482–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Osteoplus; Rebone; ***China***: An Ti Fen (安体芬); Gu Su An (固苏桉); Li La (力拉); Xin Yi Sheng (信依生); ***Ital.***: Osteofix; ***Jpn***: Osten.

Multi-ingredient Preparations. ***Arg.***: Copelia; ***India***: Calflavone; Ipridol; ***Indon.***: Vosteon; ***UK***: Osteopro.

Lasofoxifene *(BAN, rINN)* ⊗

Lasofoxifène; Lasofoxifeno; Lasofoxifenum; Лазофоксифен.

(-)-*cis*-5,6,7,8-Tetrahydro-6-phenyl-5-[*p*-[2-(1-pyrrolidinyl)ethoxy]phenyl]-2-naphthol.

$C_{28}H_{31}NO_2$=413.6

CAS — 180916-16-9.

ATC — G03XC03.

ATC Vet — QG03XC03.

UNII — 337G83N988.

The symbol † denotes a preparation no longer actively marketed

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p. viii)

Lasofoxifene Tartrate *(BANM, USAN, rINNM)* ⊗

CP-336156CB; Lasofoxifène, Tartrate de; Lasofoxifeni Tartras; Tartrato de lasofoxifeno; Лазофоксифена Тартрат.
(-)-*cis*-5,6,7,8-Tetrahydro-6-phenyl-5-[*p*-[2-(1-pyrrolidinyl) ethoxy]phenyl]-2-naphthol D-tartrate (1:1).
$C_{28}H_{31}NO_2.C_4H_6O_6$=563.6
CAS — 190791-29-8.
ATC — G03XC03.
ATC Vet — QG03XC03.
UNII — 85X09V2GSO.

NOTE. The name Fablyn has been used as a trade mark for lasofoxifene tartrate.

Profile

Lasofoxifene is a selective oestrogen receptor modulator similar to raloxifene (p. 2303.1), that was developed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

References.

1. Gennari L. Lasofoxifene, a new selective estrogen receptor modulator for the treatment of osteoporosis and vaginal atrophy. *Expert Opin Pharmacother* 2009; 10: 2209–20.
2. Cummings SR, *et al.* PEARL Study Investigators. Lasofoxifene in postmenopausal women with osteoporosis. *N Engl J Med* 2010; 362: 686–96.
3. LaCroix AZ, *et al.* PEARL Investigators. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. *J Natl Cancer Inst* 2010; 102: 1706–15.
4. Ensrud K, *et al.* Lasofoxifene and cardiovascular events in postmenopausal women with osteoporosis: five-year results from the postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial. *Circulation* 2010; 122: 1716–24.
5. Goldstein SR, *et al.* Postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial: 5-year gynecological outcomes. *Menopause* 2011; 18: 17–22.
6. Peterson GM, *et al.* Lasofoxifene: selective estrogen receptor modulator for the prevention and treatment of postmenopausal osteoporosis. *Ann Pharmacother* 2011; 45: 499–509.

Medronate

Medronic Acid *(BAN, USAN, pINN)*

Acid medronique; Acide Médronique; Ácido medrónico; Acidum medronicum; Medrónico, ácido; Медроновая Кислота.
Methylenebis(phosphonic acid).
$CH_6O_6P_2$=176.0
CAS — 1984-15-2.
UNII — 73OS0QIN3O.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Medronic Acid for Radiopharmaceutical Preparations). A white or almost white, amorphous or crystalline, hygroscopic powder. Very soluble in water; very slightly soluble in absolute alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Medronate Disodium *(USAN, pINNM)*

Disodium Medronate (BANM); Disodium Methylene Diphosphonate; MDP; Medronas Dinatricum; Médronate Disodique; Medronato disódico; Динатрий Медронат.
Disodium dihydrogen methylenediphosphonate.
$CH_4Na_2O_6P_2$=220.0
CAS — *25681-89-4.*
UNII — HAY5MT18L3.

Profile

Medronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It has a strong affinity for bone. Complexes of medronate disodium and stannous chloride or fluoride, or medronic acid, stannous chloride dihydrate, and ascorbic acid, are labelled with radioactive technetium-99m (p. 2228.1) and used diagnostically as bone scanning agents; they are given intravenously.

Hypersensitivity. For reference to a severe allergic reaction attributed to the medronate component of a radiopharmaceutical, see under Adverse Effects and Precautions of Bisphosphonates, p. 1177.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Amerscan Medronate†; *Irl.*: Medronate Draximage†; *Israel*: Prosstimage Kit (MDP).

Multi-ingredient Preparations. *Denm.*: Amerscan Stannous†.

Minodronate

Minodronic Acid *(rINN)*

Acide Minodronique; Ácido minodrónico; Acidum minodronicum; Ono-5920; YH-529; YM-529; Миндроновая Кислота.
(1-Hydroxy-2-imidazo[1,2-*a*]pyridin-3-ylethylidene)diphosphonic acid.
$C_9H_{12}N_2O_7P_2$=322.1
CAS — 127657-42-5.
UNII — 40SGR63TGL.

Profile

Minodronate is a bisphosphonate that inhibits bone resorption. It is given as minodronic acid hydrate for the treatment of osteoporosis; 1 mg is given orally once daily, usually in the morning. Specific instructions for oral use (see Precautions in Alendronate, p. 1172.3) should be followed to minimise adverse effects and permit adequate absorption.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Bonoteo; Recalbon.

Neridronate

Neridronic Acid *(rINN)*

Acide Néridronique; Ácido neridrónico; Acidum neridronicum; AHDP; AHHexBP; Aminohexane Diphosphonate; Neridrónico, ácido; Неридроновая Кислота.
(6-Amino-1-hydroxyhexylidene)diphosphonic acid.
$C_6H_{17}NO_7P_2$=277.1
CAS — 79778-41-9.
UNII — 8U27U3RIN4.

Neridronate Sodium *(rINNM)*

Natrii Neridronas; Néridronate de Sodium; Neridronato sódico; Натрий Неридронат.
UNII — H6JVB49Q0F.

Profile

Neridronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p. 1173.3). It inhibits bone resorption and is given intravenously as the sodium salt in the management of osteogenesis imperfecta (p. 1167.3); it has been used in the treatment of malignant hypercalcaemia (p. 1167.2) and diseases associated with excessive bone turnover such as Paget's disease of bone (p. 1169.3) and osteoporosis (p. 1168.1). The intramuscular route has also been used.

References.

1. O'Rourke NP, *et al.* Treatment of malignant hypercalcaemia with aminohexane bisphosphonate (neridronate). *Br J Cancer* 1994; 69: 914–17.
2. Filipponi P, *et al.* Paget's disease of bone: benefits of neridronate as a first treatment and in cases of relapse after clodronate. *Bone* 1998; 23: 543–8.
3. Adami S, *et al.* Short-term intravenous therapy with neridronate in Paget's disease. *Clin Exp Rheumatol* 2002; 20: 55–8.
4. Adami S, *et al.* Intravenous neridronate in adults with osteogenesis imperfecta. *J Bone Miner Res* 2003; 18: 126–30.
5. Braga V, *et al.* Intravenous intermittent neridronate in the treatment of postmenopausal osteoporosis. *Bone* 2003; 33: 342–5.
6. Cascella T, *et al.* Effects of neridronate treatment in elderly women with osteoporosis. *J Endocrinol Invest* 2005; 28: 202–8.
7. Gatti D, *et al.* Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled study. *J Bone Miner Res* 2005; 20: 758–63.
8. Adami S, *et al.* Intramuscular neridronate in postmenopausal women with low bone mineral density. *Calcif Tissue Int* 2008; 83: 301–7.
9. Benucci M, *et al.* Effects of monthly intramuscular neridronate in rheumatic patients in chronic treatment with low-dose glucocorticoids. *Clin Exp Rheumatol* 2009; 27: 567–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Nerixia.

Odanacatib *(USAN, rINN)*

Odanacatibum; Оданакатиб.
(2*S*)-*N*-(1-Cyanocyclopropyl)-4-fluoro-4-methyl-2-{[(1*S*)-2,2,2-trifluoro-1-[4′-(methylsulfonyl)[1,1′-biphenyl)-4-yl]ethyl] amino}pentanamide.
$C_{25}H_{27}F_4N_3O_3S$=525.6
CAS — 603139-19-1.
UNII — N673F6W2VH.

Profile

Odanacatib is a cathepsin-K inhibitor that reduces bone resorption. It is being investigated for the treatment of osteoporosis.

References.

1. Bone HG, *et al.* Odanacatib, a cathepsin-K inhibitor for osteoporosis a two-year study in postmenopausal women with low bone density. *J Bone Miner Res* 2009; 25: 937–47.
2. Lewiecki EM. Odanacatib, a cathepsin K inhibitor for the treatment of osteoporosis and other skeletal disorders associated with excessive bone remodeling. *IDrugs* 2009; 12: 799–809.

Oxidronate

Oxidronic Acid *(BAN, USAN, pINN)*

Acide Oxidronique; Ácido oxidrónico; Acidum Oxidronicum; Oxidrónico, ácido; Оксидроновая Кислота.
(Hydroxymethylene)diphosphonic acid.
$CH_6O_7P_2$=192.0
CAS — 15468-10-7.
UNII — 71MR4V32TI.

Oxidronate Disodium *(pINNM)*

Disodium Oxidronate; HMDP; Oxidronas Dinatricum; Oxidronate Disodique; Oxidronate Sodium; Oxidronato disódico; Sodium Oxidronate (BANM); Динатрий Оксидронат.
Disodium (hydroxymethylene)diphosphonate.
$CH_4Na_2O_7P_2$=236.0
CAS — 14255-61-9.
UNII — H852YK87WP.

Profile

Oxidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It has a strong affinity for bone. A chelate of oxidronate disodium with radioactive technetium-99m (p. 2228.1) is used diagnostically as a bone scanning agent; it is given intravenously.

Pamidronate

ATC — M05BA03.
ATC Vet — QM05BA03.
UNII — OYY3447OMC.

Pamidronic Acid *(BAN, rINN)*

Acide Pamidronique; Ácido pamidrónico; Acidum Pamidronicum; Aminohydroxypropylidenebisphosphonate; APD; Pamidrónico, ácido; Pamidronihappo; Pamidronsyra; Памидроновая Кислота.
3-Amino-1-hydroxypropylidenebis(phosphonic acid).
$C_3H_{11}NO_7P_2$=235.1
CAS — 40391-99-9.
ATC — M05BA03.
ATC Vet — QM05BA03.

Pamidronate Disodium *(USAN, rINNM)*

Aminohydroxypropylidenebisphosphonate Disodium; CGP-23339A; CGP-23339AE; Dinatrii Pamidronas Pentahydricus; Dinatriumpamidronaattipentahydraatti; Dinatrium-pamidronát pentahydrát; Disodium Aminohydroxypropylidenediphosphonate; Disodium Pamidronate (BANM); Disodu pamidronian pięciowodny; Disodyum Pamidronat; Pamidronaattidinatrium; Pamidronas Dinatricum; Pamidronatdinatrium; Pamidronatdinatriumpentahydrat; Pamidronate Disodique; Pamidronate disódique pentahydraté; Pamidronato disódico; Pamidronatum Dinatricum; Динатрий Памидронат.
Disodium 3-amino-1-hydroxypropylidenebisphosphonate pentahydrate.
$C_3H_9NNa_2O_7P_2.5H_2O$=369.1
CAS — 109552-15-0 (pamidronate disodium pentahydrate); 57248-88-1 (anhydrous pamidronate disodium).
ATC — M05BA03.
ATC Vet — QM05BA03.
UNII — 8742TBZQZA (pamidronate disodium pentahydrate); C7S8VWP5DH (anhydrous pamidronate disodium).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pamidronate Disodium Pentahydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in dichloromethane. It is sparingly soluble in dilute mineral acids and dissolves in dilute alkaline solutions. A 1.0% solution in water has a pH of 7.8 to 8.8.

USP 36: (Pamidronate Disodium). A white crystalline powder. Soluble in water and in 2N sodium hydroxide; sparingly soluble 0.1N acetic acid and in 0.1N hydrochloric acid; practically insoluble in organic solvents. pH of a 1% solution in water is between 7.8 and 8.8. Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Pamidronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p. 1173.3). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses.

Pamidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also used in the treatment of osteolytic lesions and bone pain in multiple myeloma or bone metastases associated with breast cancer. It may also be of benefit in bone disorders associated with excessive bone resorption, including Paget's disease of bone.

Pamidronate disodium is given by slow intravenous infusion. UK licensed product information recommends infusion at a rate not exceeding 60 mg/hour (or not exceeding 20 mg/hour in patients with established or suspected renal impairment) and at a concentration not exceeding 60 mg per 250 mL of infusion solution (sodium chloride 0.9% or glucose 5%). In the USA, the recommended concentration of infusion and rate vary depending on the indication.

In **hypercalcaemia of malignancy** pamidronate disodium is given by slow intravenous infusion in a total dose of 15 to 90 mg according to the initial plasma-calcium concentration. In the UK, the total dose is given as a single infusion or in divided doses over 2 to 4 days. In the USA, the total dose is given as a single infusion, doses of 60 mg to 90 mg being given over 2 to 24 hours. Plasma-calcium concentrations generally start declining 24 to 48 hours after a dose of pamidronate with normalisation within 3 to 7 days. Treatment may be repeated if normocalcaemia is not achieved within this time or if hypercalcaemia recurs.

In patients with **osteolytic lesions and bone pain** of multiple myeloma or bone metastases associated with breast cancer, pamidronate disodium may be given in doses of 90 mg by intravenous infusion every 3 to 4 weeks.

In the treatment of **Paget's disease** the dosage regimen in the UK is 30 mg by slow infusion once a week for 6 weeks (total dose 180 mg), or 30 mg in the first week then 60 mg every other week for 6 weeks (total dose 210 mg). These courses may be repeated every 6 months, and the total dose increased if necessary up to a maximum of 360 mg. Alternatively, the dose used in the USA is 30 mg by infusion over 4 hours, repeated on consecutive days to a total dose of 90 mg. This course is repeated when clinically indicated.

For details of administration in renal impairment, see below.

Pamidronate has also been given orally.

General references.

1. Coukell AJ, Markham A. Pamidronate: a review of its use in the management of osteolytic bone metastases, tumour-induced hypercalcaemia and Paget's disease of bone. *Drugs Aging* 1998; **12**: 149–68.

Administration in renal impairment. Pharmacokinetic studies suggest that no dosage reduction of pamidronate disodium is required in patients with any degree of renal impairment.[1] However, UK product information currently recommends that the rate of infusion be reduced to a maximum of 20 mg/hour for patients with established or suspected renal impairment; use in those with severe renal impairment (creatinine clearance less than 30 mL/minute) is not advised as clinical experience is limited.

1. Berenson JR, *et al.* Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol* 1997; **37**: 285–90.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p. 8.1). Bisphosphonates may be of benefit in controlling associated pain in some patients. In small studies, intravenous pamidronate 30 mg daily for 3 days, or at 1 mg/kg daily for 1 or 3 days,[1] or 60 mg daily for 3 days,[2] significantly improved pain and range of movement in cases refractory to previous treatment.

1. Maillefert JF, *et al.* Pooled results from 2 trials evaluating bisphosphonates in reflex sympathetic dystrophy. *J Rheumatol* 1999; **26**: 1856–7.
2. Kubalek I, *et al.* Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases. *Rheumatology (Oxford)* 2001; **40**: 1394–7.

Gaucher disease. Treatment with oral pamidronate disodium in doses of 600 mg daily in adults,[1] and 150 to 300 mg daily in children,[2] or intravenous pamidronate disodium in doses of 45 mg every 3 weeks,[3] has been reported to improve bone lesions of Gaucher disease (p. 2433.3) in a few patients.

1. Harinck HIJ, *et al.* Regression of bone lesions in Gaucher's disease during treatment with aminohydroxypropylidene bisphosphonate. *Lancet* 1984; **ii**: 513.
2. Samuel R, *et al.* Aminohydroxy propylidine bisphosphonate (APD) treatment improves the clinical skeletal manifestations of Gaucher's disease. *Pediatrics* 1994; **94**: 385–9.
3. Ciana G, *et al.* Short-term effects of pamidronate in patients with Gaucher's disease and severe skeletal involvement. *N Engl J Med* 1997; **337**: 712.

Hypercalcaemia. Bisphosphonates, of which pamidronate is one of the most effective, are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Pamidronate is licensed for such use in many countries. A literature review[1] of phase II and III studies concluded that pamidronate was effective in the treatment of pain and skeletal complications from metastatic disease, particularly in patients with breast cancer or multiple myeloma, but that its efficacy in those with other neoplasms needed confirmation. A long-term follow-up[2] of 2 randomised trials of pamidronate in women with breast cancer confirmed its efficacy over placebo. However, a pooled analysis[3] of its use for palliation of bone pain in men with metastatic prostate cancer found no treatment benefit with pamidronate over placebo. A meta-analysis[4] confirmed the benefits of the bisphosphonate in reducing skeletal events, and hence morbidity, in patients with cancer, but not mortality; however, no clear advantage could be shown versus clodronate or zoledronate, which were also of benefit. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Ripamonti C, *et al.* Role of pamidronate disodium in the treatment of metastatic bone disease. *Tumori* 1998; **84**: 442–55.
2. Lipton A, *et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; **88**: 1082–90.
3. Small EJ, *et al.* Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003; **21**: 4277–84.
4. Machado M, *et al.* Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009; **31**: 962–79.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including pamidronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Osteogenesis imperfecta. Pamidronate has produced benefit in patients with osteogenesis imperfecta (p. 1167.3). Although the dosage and timing varied between centres and age groups, all patients were given cyclical intravenous pamidronate;[1-6] bone mineral density increased, fracture incidence decreased, and patients reported improvements in mobility, pain and chronic fatigue. Treated infants achieved motor milestones earlier than untreated controls; vertebral height was also improved.[5] While bone size and density also increased in patients given pamidronate, especially in those with larger baseline deficits in bone mass,[7] serum calcium decreased markedly, and bone turnover was suppressed;[8] clinical problems were not evident if calcium intake was sufficient, but consequences of a chronically low bone turnover are unknown. A study in young patients found that bone metabolism is still suppressed, and that bone mass gains continue, for 2 years after stopping therapy.[9]

1. Glorieux FH, *et al.* Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998; **339**: 947–52.
2. Plotkin H, *et al.* Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab* 2000; **85**: 1846–50.
3. Åström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002; **86**: 356–64.
4. Falk MJ, *et al.* Intravenous bisphosphonate therapy in children with osteogenesis imperfecta. *Pediatrics* 2003; **111**: 573–8.
5. Åström E, *et al.* Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. *Arch Dis Child* 2007; **92**: 332–8.
6. Senthilnathan S, *et al.* Two doses of pamidronate in infants with osteogenesis imperfecta. *Arch Dis Child* 2008; **93**: 398–400.
7. Rauch F, *et al.* Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. *J Bone Miner Res* 2003; **18**: 610–14.
8. Rauch F, *et al.* Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. *J Clin Endocrinol Metab* 2003; **88**: 986–92.
9. Rauch F, *et al.* Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J Clin Endocrinol Metab* 2006; **91**: 1268–74.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p. 1168.1). A placebo-controlled trial of oral pamidronate 150 mg daily found it to be effective in increasing bone mineral density (BMD) of the lumbar spine and femoral neck in both **men** and **women**.[1] Intravenous pamidronate at 30 mg every 3 months, or 60 mg every 6 months, also increased BMD in the lumbar spine, femoral neck, and trochanter in an observational, retrospective study.[2] Single intravenous infusions of pamidronate given every 3 months have also been reported to increase BMD and reduce fracture rates in **children** with osteoporosis;[3,4] annual doses were in the region of 4 mg/kg.

An open study[5] in men with prostate cancer (but no bone metastases) and receiving leuprorelin, found that addition of pamidronate 60 mg intravenously every 12 weeks prevented **therapy-induced** bone loss in the hip and lumbar spine. Acute bone loss from the femur and pelvis after hip arthroplasty was also reduced by a single infusion of 90 mg pamidronate in a small prospective study.[6] Similarly, in premenopausal women with chemotherapy-induced bone loss, pamidronate 60 mg intravenously every 3 months prevented bone loss at the spine and hip compared with placebo.[7]

In a small study[8] of patients receiving **corticosteroids**, pamidronate given intravenously either as a single infusion of 90 mg, or as 90 mg followed by 30 mg every 3 months for 1 year, significantly increased BMD at the lumbar spine, femoral neck, and total hip. In lymphoma patients receiving corticosteroids as part of chemotherapy regimens, pamidronate 30 mg intravenously every 3 months reduced bone loss when compared with placebo.[9] Pamidronate has shown beneficial increases in or preservation of BMD in patients after heart,[10,11] liver,[11] lung,[12] or stem cell[13] transplantation.

1. Brumsen C, *et al.* Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. *J Bone Miner Res* 2002; **17**: 1057–64.
2. Chan SSY, *et al.* Intravenous pamidronate in the treatment and prevention of osteoporosis. *Intern Med J* 2004; **34**: 162–6.
3. Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. *J Pediatr* 2003; **142**: 417–23.
4. Gandrud LM, *et al.* Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. *J Pediatr Endocrinol Metab* 2003; **16**: 887–92.
5. Smith MR, *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; **345**: 948–55.
6. Wilkinson JM, *et al.* Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial. *J Bone Miner Res* 2001; **16**: 556–64.
7. Fuleihan GE-H, *et al.* Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90**: 3209–14.
8. Boutsen Y, *et al.* Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001; **16**: 104–12.
9. Kim SH, *et al.* Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. *Am J Med* 2004; **116**: 524–8.
10. Krieg MA, *et al.* Intravenous pamidronate as treatment for osteoporosis after heart transplantation: a prospective study. *Osteoporosis Int* 2001; **12**: 112–16.
11. Dodidou P, *et al.* Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. *Osteoporosis Int* 2003; **14**: 82–9.
12. Cahill BC, *et al.* Prevention of bone loss and fracture after lung transplantation: a pilot study. *Transplantation* 2001; **72**: 1251–5.
13. Grigg AP, *et al.* Pamidronate reduces bone loss after allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2006; **91**: 3835–43.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Pamidronate was initially used orally for Paget's disease, but intravenous therapy has been preferred because of a lower incidence of adverse effects.[1,2] With the usual total dose of 180 mg, remission is considered likely in most patients with mild to moderate disease, but unlikely if disease is severe.[2] However, higher doses (about 340 mg) were found to be effective in those with very active disease, and also associated with a longer remission.[1] In a 2-year study[3] of 3 different doses, pamidronate increased bone mineral density in pagetic bone of the lumbar spine, femoral neck, and total hip, but lacked this effect on non-pagetic bone in the same areas; loss of density was apparent in non-pagetic forearm bone in the group given the highest dose (240 mg). Patients with coexistent osteoarthritis or arthropathy responded less well to pamidronate in terms of pain perception, than those patients without joint disease.[4] While hearing loss may or may not improve with pamidronate,[5,6] there has been a report of successful treatment of optic neuropathy due to Paget's disease with pamidronate and dexamethasone.[7] Bisphosphonates have also been given in other bone diseases with a similar pathology, particularly increased osteoclastic resorption. For example, pamidronate has had beneficial effects in patients with fibrous dysplasia of bone, a rare congenital disease leading to osteolytic lesions.[8-10]

1. Selby PL. Pamidronate in the treatment of Paget's disease. *Bone* 1999; **24**: 575–585.
2. Tucci JR, Bontha S. Intravenously administered pamidronate in the treatment of Paget's disease of bone. *Endocr Pract* 2001; **7**: 423–9. Correction. *ibid.* 2002; **8**: 78.
3. Gutteridge DH, *et al.* Bone density changes in Paget's disease 2 years after iv pamidronate: profound, sustained increases in pagetic bone with

severity-related loss in forearm nonpagetic cortical bone. *Bone* 2003; 32: 56–61.
4. Vasireddy S, *et al.* Patterns of pain in Paget's disease of bone and their outcomes on treatment with pamidronate. *Clin Rheumatol* 2003; 22: 376–80.
5. Donáth J, *et al.* Effect of bisphosphonate treatment in patients with Paget's disease of the skull. *Rheumatology (Oxford)* 2004; 43: 89–94.
6. Murdin L, Yeoh LH. Hearing loss treated with pamidronate. *J R Soc Med* 2005; 98: 272–4.
7. Isasi C, *et al.* Successful treatment of optic neuropathy in osteitis deformans. *Rheumatology (Oxford)* 2002; 41: 948–50.
8. Liens D, *et al.* Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet* 1994; 343: 953–4.
9. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. *J Pediatr* 2000; 137: 403–9.
10. Plotkin H, *et al.* Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *J Clin Endocrinol Metab* 2003; 88: 4569–75.

Rheumatoid arthritis and spondyloarthropathies. Intravenous[1] and oral[2] use of pamidronate has reportedly produced some modification of disease in a few patients with rheumatoid arthritis (p. 13.2). Continuous oral pamidronate therapy was shown to be effective in preserving and increasing bone mass in a 3-year randomised controlled trial involving 105 patients with rheumatoid arthritis.[3] In contrast, a small controlled study[4] in 26 patients found no significant effect on rheumatoid arthritis disease activity with intravenous pamidronate. There are reports of an analgesic response to pamidronate in patients with acute rheumatic pain of various aetiologies, including arthritis and ankylosing spondylitis, and a trial[5] in patients with ankylosing spondylitis found a dose-dependent therapeutic effect with pamidronate.[6] Use of intravenous pamidronate and methylprednisolone has also been investigated as part of the management of patients with NSAID-unresponsive ankylosing spondylitis.[7]

1. Eggelmeijer F, *et al.* Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. *J Rheumatol* 1994;21: 2016–20.
2. Maccagno A, *et al.* Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand J Rheumatol* 1994; 23: 211–14.
3. Eggelmeijer F, *et al.* Increased bone mass with pamidronate treatment in rheumatoid arthritis: results of a three-year randomized, double-blind trial. *Arthritis Rheum* 1996; 39: 396–402.
4. Lodder MC, *et al.* Effects of high dose intravenous pamidronate on disease activity and bone metabolism in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2003; 30: 2080–1.
5. El-Shafei A, *et al.* Is pamidronate effective for acute rheumatic pain? *Ann Rheum Dis* 2002; 61: 183.
6. Maksymowych WP, *et al.* A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; 46: 766–73.
7. Malaviya AN, *et al.* A new strategy of drug treatment in NSAID-unresponsive ankylosing spondylitis: combination of pamidronate and methylprednisolone monthly intravenous infusions on the background of a combination of disease modifying drugs sulfasalazine and methotrexate. *J Assoc Physicians India* 2007; 55: 193–7.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3.

Fever and flu-like symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes) are common during intravenous infusion of pamidronate but generally resolve spontaneously. Pamidronate should not be given by bolus injection, as severe local reactions and thrombophlebitis have occurred. CNS effects include agitation, confusion, dizziness, lethargy, insomnia, and somnolence. There have been isolated cases of seizures, and visual hallucinations. In addition to hypocalcaemia and hypophosphataemia, which are common, hypomagnesaemia or hypokalaemia may occur, and rarely, hypernatraemia, or hyperkalaemia. Both hypotension and hypertension have been reported. Anaemia, thrombocytopenia, and lymphocytopenia may occur. Bronchospasm and interstitial pneumonitis have occurred rarely.

Pamidronate should be used with caution in those with cardiac disease, because of the potential for fluid overload, and in those who have had thyroid surgery, because of the increased risk of hypocalcaemia due to relative hypoparathyroidism. Serum electrolytes, calcium and phosphate should be monitored during therapy, along with renal function. Patients should be warned against driving or operating machinery after treatment if somnolence or dizziness occur.

Effects on the ears. Ototoxicity, manifest as tinnitus and sudden hearing loss, has been reported[1] in 2 patients given both intravenous and oral pamidronate for pre-existing otosclerosis.[1] A patient given 5 pamidronate infusions for Paget's disease developed tinnitus, vertigo, and hearing loss; the latter two symptoms resolved over 9 months, but tinnitus persisted.[2]

1. Boumans LJJM, Poublon RML. The detrimental effect of aminohydroxypropylidene bisphosphonate (APD) in otospongiosis. *Eur Arch Otorhinolaryngol* 1991; 248: 218–21.
2. Reid IR, *et al.* Ototoxicity associated with intravenous bisphosphonate administration. *Calcif Tissue Int* 1995; 56: 584–5.

Effect on electrolytes. Pamidronate has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in 2 patients. In each case, other conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; 328: 335–6.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including pamidronate, see under Bisphosphonates, p. 1175.2.

Effects on the gastrointestinal tract. The tolerability of pamidronate given *orally* may depend to some extent on the particular formulation. Gastrointestinal disturbances (in 21.8%) and haematological abnormalities (in 9.4%) were the main adverse effects associated with oral pamidronate in an open study of elderly patients.[1] Oesophagitis, noted earlier[2] in 4 of 49 patients given a different formulation, was not reported in this study.[1]

1. Spivacow FR, *et al.* Tolerability of oral pamidronate in elderly patients with osteoporosis and other metabolic bone diseases. *Curr Ther Res* 1996; 57: 123–30.
2. Lufkin EG, *et al.* Pamidronate: an unrecognised problem in gastrointestinal tolerability. *Osteoporosis Int* 1994; 4: 320–2.

Effects on the kidneys. Like other bisphosphonates (see p. 1176.1), pamidronate may cause adverse renal effects. UK licensed product information notes that there have been isolated cases of haematuria, acute renal failure, and deterioration of pre-existing renal disease. Renal function should be monitored during long-term pamidronate therapy, especially in patients with pre-existing renal disease or a predisposition to renal impairment. Longer infusion times may reduce the risk of renal toxicity, and various infusion rates have been recommended, see Uses and Administration, p. 1187.1.

Effects on mental state. Palpitations, followed by visual hallucinations, suicidal ideation, and clinical depression were reported in an elderly man after a single infusion of pamidronate for Paget's disease; he had no previous psychiatric history. Treatment with thioridazine reduced the frequency and effect of the hallucinations.[1]

1. Foley-Nolan D, *et al.* Pamidronate associated hallucinations. *Ann Rheum Dis* 1992; 51: 927–8.

Effects on the musculoskeletal system. Although pamidronate appears to be a less potent inhibitor of bone mineralisation than etidronate, mineralisation defects have been reported in patients with Paget's disease of bone receiving pamidronate.[1] The resultant osteomalacia was not associated with any adverse clinical effects. Pamidronate-induced osteopetrosis has also been reported.[2] Acute pseudogout arthritis in a woman treated with pamidronate for acute hypercalcaemia was possibly due to deposition of calcium in the joints.[3] Severe bone pain occurred in more patients than expected when pamidronate was used for treatment of low bone density in cystic fibrosis;[4] an increase in proinflammatory cytokines was postulated as a mechanism for this effect.[5]

Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

1. Adamson BB, *et al.* Mineralisation defects with pamidronate therapy for Paget's disease. *Lancet* 1993; 342: 1459–60.
2. Whyte MP, *et al.* Bisphosphonate-induced osteopetrosis. *N Engl J Med* 2003; 349: 457–63.
3. Malnick SDH *et al.* Acute pseudogout as a complication of pamidronate. *Ann Pharmacother* 1997; 31: 499–500.
4. Haworth CS, *et al.* Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. *Lancet* 1998; 352: 1753–4.
5. Teramoto S, *et al.* Increased cytokines and pamidronate-induced bone pain in adults with cystic fibrosis. *Lancet* 1999; 353: 750.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. Rash and pruritus occasionally follow pamidronate infusion. Mild skin rashes have also been reported in some patients taking oral pamidronate (see also under Bisphosphonates, p. 1177.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pamidronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Bisphosphonates cross the placenta in animals and humans. These drugs also persist in mineralised bone for many years. Thus, in theory, even if use were to be avoided during pregnancy, the fetus might still be exposed to bisphosphonates from prior therapy released from the maternal skeleton. Furthermore, suppressed bone turnover caused by residual bisphosphonate might cause maternal complications during pregnancy.[1] However, no adverse effects were seen during pregnancy in 2 women with osteogenesis imperfecta given intravenous pamidronate before conception. One infant had transient asymptomatic hypocalcaemia, and one had bilateral talipes equinovarus (a congenital deformity in which the foot turns downwards and inwards). No other skeletal abnormalities were noted. The authors advised monitoring of neonatal calcium concentrations in infants born to mothers treated with pamidronate.[1] In another report of 3 women given long-term pamidronate before conception, 4 healthy infants were born with no evidence of biochemical or skeletal abnormalities.[2]

1. Munns CFJ, *et al.* Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. *J Bone Miner Res* 2004; 19: 1742–5.
2. Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. *J Clin Endocrinol Metab* 2006; 91: 2017–20.

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Plasma concentrations of pamidronate rise rapidly after the start of an intravenous infusion; the apparent plasma half-life is 0.8 hours. Plasma protein binding is about 54%. Pamidronate is not metabolised, and about 20 to 55% of the dose is excreted in the urine unchanged within 72 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment and infusion rates may need to be reduced (see p. 1187.1).

Like all bisphosphonates, oral pamidronate is poorly absorbed from the gastrointestinal tract; bioavailability is about 1 to 3%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aminomux; Pamdosa; Pandrat; *Austral.*: Aredia; Pamisol; *Austria*: Aredia; Ebedronat; Pamidro-Cell†; Pamitor; *Belg.*: Aredia; Pamidrin; *Braz.*: Aredia; Pauldpami; Pamidrom; Pamired; *Canad.*: Aredia; *Chile*: Aminomux†; Pamifos; *China*: Aredia (阿可达); Boning (博宁); Ren Yi (仁怡); *Cz.*: Aredia†; Pamitor; *Denm.*: Aredia†; Pamifos; *Fin.*: Aredia†; Pamifos; *Fr.*: Aredia†; Ostepam; Paminject†; *Ger.*: Aredia; Axidronat; Novapam; Pamidro-cell; Pamidron†; Pamifos; Ribodronat; *Gr.*: Aredia; Pamerit; Pamidrone; *Hong Kong*: Aredia; Pamisol; *Hung.*: Aredia; Pamifos; Pamitor; *India*: Aredia; Aredronet; Bonapam; Pamidria; Pamidro; Pamifos; *Indon.*: Aredia†; Pamired; *Irl.*: Aredia; *Israel*: Aredia; *Ita.*: Amidrox†; Aredia; Texpami†; *Jpn*: Aredia; *Malaysia*: Aredia; Pamired; Pamisol; *Mex.*: Aredia; Pamisol; *Neth.*: Pamipro; *N.Z.*: Pamisol; *Philipp.*: Aredia; *Pol.*: Aredia; Pamidia; Pamifos; Pamsol; Pamitor; *Port.*: Pamidran; *Rus.*: Aredia (Аредиа); Pomegara (Помегара); *S.Afr.*: Aredia; *Singapore*: Aredia; Pamired; Pamsol; *Spain*: Aredia; Linoten†; Pamifos†; *Swed.*: Aredia†; Pamfos; *Switz.*: Aredia; Pamidron†; Pamifos†; *Thai.*: Aredia; Pamsol; *Turk.*: Aredia; Pamex; Pamidem; *UK*: Aredia; *Ukr.*: Aredia (Аредиа); Pamired (Памиред); *USA*: Aredia†; *Venez.*: Aminomux.

Pharmacopoeial Preparations
BP 2014: Pamidronate Disodium Infusion;
USP 36: Pamidronate Disodium for Injection.

Parathyroid Hormone *(BAN, USAN, rINN)*

1-84 Parathormone; ALX1-11 (human recombinant parathyroid hormone); Hormona paratiroidea; Hormone Parathyroïde; Hormonum Parathyroidum; Parathormone; Parathyrin; Parathyroid hormone (1-84); Paratirina; PTH; PTH (1-84); Паратиреоидный гормон.

CAS — 9002-64-6; 68893-82-3 (human parathyroid hormone); 345663-45-8 (human recombinant parathyroid hormone).
ATC — H05AA03.
ATC Vet — QH05AA03.
UNII — N19A0T0E5J.

Uses and Administration

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first (N-terminal) 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Endogenous parathyroid hormone is involved in the maintenance of plasma-calcium concentrations through its actions on bone, kidney, and indirectly on the gastrointestinal tract (see also under Parathyroid Disorders, p. 1170.3).

Exogenous parathyroid hormone was formerly used in acute hypoparathyroidism with tetany. It has also been used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism. A human recombinant form is

under investigation for the treatment of hypoparathyroidism.

The human recombinant form is used for the treatment of osteoporosis in postmenopausal women at high risk of fractures. The recommended dose is 100 micrograms once daily, given by subcutaneous injection into the abdomen; treatment may be continued for up to 24 months. Supplemental calcium and vitamin D may be needed if dietary intake is inadequate. However, if serum calcium becomes persistently raised, and there is no underlying disease, calcium and vitamin D should be withdrawn, and parathyroid hormone dosing changed to 100 micrograms on every other day. If elevated concentrations persist, parathyroid hormone therapy should be stopped until values return to normal.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones are now used for diagnostic purposes, and for the treatment of osteoporosis (see Teriparatide, p. 1191.2).

References.
1. Rittmaster RS, *et al.* Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 2000; **85**: 2129–34.
2. Hodsman AB, *et al.* Efficacy and safety of human parathyroid hormone-(1–84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88**: 5212–20.
3. Anonymous. ALX 111: ALX1-11, parathyroid hormone (1-84)–NPS Alleilx, PREOS, PTH, recombinant human parathyroid hormone, rhPTH (1-84). *Drugs R D* 2003; **4**: 231–9.
4. White H, Ahmad A. PREOS NPS (Alleilx/Nycomed). *Curr Opin Investig Drugs* 2005; **6**: 1057–66.
5. Shrader SP, Ragucci KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother* 2005; **39**: 1511–16.
6. Moen MD, Scott LJ. Recombinant full-length parathyroid hormone (1-84). *Drugs* 2006; **66**: 2371–81; discussion 2382–5.
7. Greenspan SL, *et al.* Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med* 2007; **146**: 326–39.

Administration in renal or hepatic impairment. UK licensed product information states that no dose adjustment is necessary for parathyroid hormone when it is used in patients with mild to moderate renal or hepatic impairment, defined as those with a creatinine clearance of 30 to 80 mL/minute, and a total score of 7 to 9 on the Child-Pugh scale, respectively. Use in severe renal or hepatic impairment is not recommended due to lack of data.

Adverse Effects, Treatment, and Precautions

Transient hypercalcaemia and hypercalciuria are very common with parathyroid hormone treatment; persistent hypercalcaemia may necessitate dose reduction or withdrawal of therapy (see Uses and Administration, p. 1188.3). Patients should be monitored at months 1, 3, and 6 for elevated concentrations of serum or urinary calcium; monitoring beyond 6 months is not considered necessary for those whose serum calcium is within normal limits at 6 months. On injection, serum calcium concentrations reach a maximum after 6 to 8 hours, returning to baseline after 20 to 24 hours; blood samples for monitoring should thus be taken at least 20 hours after the most recent dose. Gastrointestinal disturbances, especially nausea, also occur commonly, as do headache, dizziness, fatigue, palpitations, muscle cramps, extremity or back pain, and injection site erythema. Hyperuricaemia has also been reported.

Pharmacokinetics

Subcutaneous parathyroid hormone produces peak plasma concentrations 1 to 2 hours after injection. The average half-life is about 1.5 hours and the absolute bioavailability is about 55%. Parathyroid hormone is removed from the blood by a receptor-mediated process in the liver and broken down into smaller peptide fragments, which either undergo further degradation within the cell or are released back into the blood and renally cleared.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Preotact; ***Cz.***: Preotact; ***Denm.***: Preotact†; ***Fr.***: Preotact†; ***Ger.***: Preotact; ***Gr.***: Preotact; ***Irl.***: Preotact; ***Ital.***: Preotact; ***Neth.***: Preotact; ***Norw.***: Preotact; ***Pol.***: Preotact; ***Port.***: Preotact; ***Spain***: Preotact; ***Swed.***: Preotact†; ***UK***: Preotact.

Plicamycin *(BAN, USAN, rINN)*

A-2371; Aureolic Acid; Mithramycin; Mithramycinum; Mitramycin; Mitramysilnl; NSC-24559; PA-144; Plicamicina; Plicamycine; Plicamycinum; Пликамицин.

$C_{52}H_{76}O_{24}$=1085.2

CAS — 18378-89-7.

ATC — L01DC02.

ATC Vet — QL01DC02.

UNII — NIJ123W41V.

Description. Plicamycin is an antineoplastic antibiotic produced by the growth of *Streptomyces argillaceus, S. plicatus* and *S. tanashiensis*.

Pharmacopoeias. In *US*.

USP 36: (Plicamycin). A yellow, odourless, hygroscopic, crystalline powder, with a potency of not less than 900 micrograms/mg, calculated on the dry basis. It loses not more than 8% of its weight when dried. Slightly soluble in water and in methyl alcohol; very slightly soluble in alcohol; freely soluble in ethyl acetate. A 0.05% solution in water has a pH of 4.5 to 5.5. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Profile

Plicamycin is a highly toxic antibiotic with antineoplastic and hypocalcaemic properties. It may act by complexing with DNA in the presence of divalent cations and inhibiting synthesis of ribonucleic acid. Lowering of serum calcium concentrations has been suggested to result from antagonism of the effects of vitamin D and parathyroid hormone on osteoclasts.

Plicamycin has been used in the symptomatic management of hypercalcaemia and hypercalciuria associated with malignancy if it cannot be managed by other means (see below). It has also been used in the treatment of malignant neoplasms of the testis not susceptible to surgery or radiotherapy; however, other agents are preferred (p. 715.1).

The major adverse effect of plicamycin is a dose-related bleeding syndrome, manifest initially as epistaxis, which may progress to haematemesis and potentially fatal haemorrhage. Severe thrombocytopenia may also occur due to bone-marrow depression. Gastrointestinal effects are common and other adverse effects include fever, malaise, drowsiness, lethargy and weakness, headache, depression, skin rashes, facial flushing, and reduced serum concentrations of calcium, phosphorus, and potassium. There may also be reversible impairment of renal and hepatic function.

Extravasation of plicamycin solutions may cause local irritation, cellulitis, and phlebitis.

Hypercalcaemia. Where treatment is required for hypercalcaemia it is aimed at increasing urinary excretion of calcium and maintaining adequate hydration. Drugs that inhibit bone resorption may also be used if hypercalcaemia is severe, particularly when it is associated with malignancy (see p. 1167.2). Plicamycin is highly toxic, and the bisphosphonates and calcitonins are generally preferred; however, it has been given in a dose of 25 micrograms/kg intravenously over 4 to 6 hours.[1,2] Although a single dose might be sufficient to normalise the serum calcium concentration, the dose can be repeated several times at intervals of 24 to 72 hours.

1. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326**: 1196–1203.
2. Hall TG, Schaliff RAB. Update on the medical treatment of hypercalcemia of malignancy. *Clin Pharm* 1993; **12**: 117–25.

Paget's disease of bone. Plicamycin has been used as a second- or third-line drug in the therapy of Paget's disease of bone (p. 1169.3), reserved for patients refractory to other treatment. Nonetheless, occasional successes are reported: one patient with refractory Paget's disease had apparent cure of her symptoms after treatment with plicamycin 25 micrograms/kg daily for 15 doses, followed by 1500 micrograms weekly for about 2 months and every 2 weeks for 6 weeks.[1] She had remained asymptomatic for 18 years after treatment. However, similar regimens have been used in other patients without this degree of success.[1] Another patient, who was refractory to calcitonin and pamidronate therapy, showed a considerable improvement in pain relief and biochemical parameters when treated with 30 micrograms/kg plicamycin daily for 3 days.[2]

1. Ryan WG, *et al.* Apparent cure of Paget's disease of bone. *Am J Med* 1990; **89**: 825–6.
2. Wimalawansa SJ. Dramatic response to plicamycin in a patient with severe Paget's disease refractory to calcitonin and pamidronate. *Semin Arthritis Rheum* 1994; **23**: 267.

Preparations

Pharmacopoeial Preparations
USP 36: Plicamycin for Injection.

Risedronate

Risedronaatti; Risedronat; Risedronatum.

ATC — M05BA07.

ATC Vet — QM05BA07.

Risedronic Acid *(BAN, rINN)*

Acide Risédronique; Ácido risedrónico; Acidum Risedronicum; Risedrónico, ácido; Ризедроновая Кислота.

[1-Hydroxy-2-(3-pyridinyl)ethylidene]diphosphonic acid.

$C_7H_{11}NO_7P_2$=283.1

CAS — 105462-24-6.

ATC — M05BA07.

ATC Vet — QM05BA07.

UNII — KM2Z91756Z.

Risedronate Sodium *(BANM, USAN, rINNM)*

Monosodium Risedronate; Natrii Risedronas; NE-58095; Risedronat Sodyum; Risédronate de Sodium; Risedronato sódico; Sodium Risedronate; Натрий Ризедронат.

Sodium trihydrogen [1-hydroxy-2-(3-pyridyl)ethylidene] diphosphonate.

$C_7H_{10}NNaO_7P_2$=305.1

CAS — 115436-72-1.

ATC — M05BA07.

ATC Vet — QM05BA07.

UNII — OFG5EXG60L.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Risedronate Sodium 2.5-Hydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides and mineral acids. pH of a 1% solution in water is 4.0 to 5.0.

USP 36: (Risedronate Sodium). A white to off-white powder. Soluble in water and in aqueous solutions; insoluble in common organic solvents.

Uses and Administration

Risedronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p. 1173.3). It inhibits bone resorption and is used either alone or with calcium, or with calcium and vitamin D for the prevention and treatment of postmenopausal osteoporosis. It is also used for the treatment of osteoporosis in men. Risedronate is also used for prevention and treatment of corticosteroid-induced osteoporosis, and for the treatment of Paget's disease of bone.

Risedronate is given orally as the sodium salt. The specific instructions given in Adverse Effects and Precautions, p. 1190.1 should be followed to minimise gastrointestinal adverse effects and permit adequate absorption. The recommended dosage for **Paget's disease** of bone is 30 mg of risedronate sodium once daily for 2 months. Treatment may be repeated once if necessary after an interval of a further 2 months. The recommended dosage for the treatment or prevention of postmenopausal or corticosteroid-induced **osteoporosis** is 5 mg daily. Alternatively, for postmenopausal osteoporosis, 35 mg may be taken once weekly, 75 mg may be taken on 2 consecutive days of each month, or 150 mg may be taken once a month. For men with osteoporosis, the recommended dose is 35 mg once weekly.

For details of administration in renal impairment, see below.

General references.
1. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161**: 353–60.
2. Dunn CJ, Goa KL. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* 2001; **61**: 685–712.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23**: 1409–21.
4. White NJ, Perry CM. Risedronate once a week. *Treat Endocrinol* 2003; **2**: 415–20.

Administration. A procedure for the extemporaneous preparation of an oral solution from risedronate tablets has been proposed,[1] for use in patients who cannot swallow whole tablets or require feeding tubes.

1. Dansereau RJ, Crail DJ. Extemporaneous procedures for dissolving risedronate tablets for oral administration and for feeding tubes. *Ann Pharmacother* 2005; **39**: 63–7.

Administration in renal impairment. Renal clearance of risedronate significantly correlated to renal function in a pharmacokinetic study,[1] although the authors concluded that generally no dosage adjustment appears necessary for patients with mild to moderate renal impairment (creatinine clearance (CC) greater than 20 mL/minute). Licensed product information states that no dosage adjustment is necessary when CC is greater than 30 mL/minute; however, use of risedronate is contra-indicated in patients with severe renal impairment (CC less than 30 mL/minute), due to a lack of clinical data.

1. Mitchell DY, *et al.* Effect of renal function on risedronate pharmacokinetics after a single oral dose. *Br J Clin Pharmacol* 2000; **49**: 215–22.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Risedronate improves bone mineral density (BMD) and reduces the risk of both vertebral and non-vertebral fractures in **postmenopausal** osteoporosis;[1-4] effects are maintained for at least 5 years.[5] In **corticosteroid-induced** osteoporosis, risedronate increases BMD at the lumbar spine, femoral neck, and trochanter.[5,6] Risedronate is also used to treat **men** with osteoporosis. In a controlled study in elderly men after a stroke, those given risedronate had increased BMD and a decreased risk of hip fracture.[7] In a prospective controlled study, 12 months of daily risedronate significantly increased BMD at the lumbar spine, femoral neck, and hip, and significantly reduced the incidence of new vertebral fractures in men with primary or secondary osteoporosis.[8]

A once-monthly regimen of risedronate was found to be similar in efficacy and safety to the once-daily regimen.[9]

1. Sickels JM, Nip C-S. Risedronate for the prevention of fractures in postmenopausal osteoporosis. *Ann Pharmacother* 2002; 36: 664–70.
2. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; 161: 353–60.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; 23: 1409–21.
4. Wells G, *et al.* Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/04/08).
5. Sorensen OH, *et al.* Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003; 32: 120–6.
6. Dougherty JA. Risedronate for the prevention and treatment of corticosteroid-induced osteoporosis. *Ann Pharmacother* 2002; 36: 512–16.
7. Sato Y, *et al.* Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med* 2005; 165: 1743–8.
8. Ringe JD, *et al.* Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 2006; 26: 427–31.
9. Delmas PD, *et al.* Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. *Bone* 2008; 42: 36–42.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Risedronate has been found to improve pagetic bone lesions,[1] and to be more effective than etidronate.[2]

1. Brown JP, *et al.* Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. *Bone* 2000; 26: 263–7.
2. Miller PD, *et al.* A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; 106: 513–20.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. The most frequent adverse effects during risedronate therapy are arthralgia and gastrointestinal disturbances. To minimise the risk of gastrointestinal effects precautions similar to those for alendronate should be observed (see p. 1172.3), although UK licensed product information allows for the tablets to be taken other than on rising (but not at bedtime or within 2 hours of food or drink). Hypocalcaemia should be corrected before beginning risedronate therapy.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, including risedronate, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including risedronate, see under Bisphosphonates, p. 1175.2.

Effects on the gastrointestinal tract. Although, like other oral bisphosphonates, it is recommended that risedronate be taken with care (see above) to avoid gastrointestinal effects, pooled analysis of 9 studies involving 10 068 patients receiving risedronate 5 mg daily indicated that the drug was not associated with an increased frequency of upper gastrointestinal effects, even among patients at increased risk due to active gastrointestinal disease or treatment with aspirin or NSAIDs as well.[1] However, it was noted that comprehensive postmarketing data would be required to see how these results would be reflected in clinical practice. Studies in women previously intolerant to alendronate found that risedronate 5 mg daily[2] and 30 mg once weekly[3] were well tolerated.

In 2 large trials, male and female patients with mild to moderate osteoarthritis of the knee were given risedronate 5 mg once daily, 15 mg once daily, 35 mg once weekly, 50 mg once weekly, or placebo. Patients were allowed continued use of aspirin or NSAIDs. Again, pooled analysis found no increased frequency of upper gastrointestinal adverse events in those given risedronate, even in those patients considered at increased risk for such events.[4]

1. Taggart H, *et al.* Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* 2002; 77: 262–70. Correction. *ibid.*; 601.
2. Adachi JD, *et al.* Tolerability of risedronate in postmenopausal women intolerant of alendronate. *Aging (Milano)* 2001; 13: 347–54.
3. Delaney MF, *et al.* Bone density changes with once weekly risedronate in postmenopausal women. *J Clin Densitom* 2003; 6: 45–50.
4. Adami S, *et al.* Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; 80: 1278–85.

Effects on the heart. For discussion of a possible increased risk of serious atrial fibrillation with bisphosphonates, including risedronate, see Effects on the Heart, under Bisphosphonates, p. 1175.3.

Effects on the musculoskeletal system. From the initial marketing of risedronate until June 2003, the FDA had received 6 reports of severe bone, joint, or muscle pain. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[1]

Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, including risedronate, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

1. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; 165: 346–7.

Effects on the respiratory system. For a report of bronchiolitis obliterans organising pneumonia induced by risedronate, see p. 1177.1.

Hypersensitivity. Allergic reactions to bisphosphonates are rare, see p. 1177.1. Angioedema, generalised rashes, and bullous skin reactions, some severe, have been reported with risedronate.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies risedronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Like other bisphosphonates, risedronate is poorly absorbed orally. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The mean bioavailability is 0.63% in the fasting state, and is reduced by 30% when given 1 hour before breakfast, and by 55% when given half an hour before breakfast. Plasma protein binding is about 24%. Risedronate is not metabolised. About half of the absorbed portion is excreted in the urine within 24 hours; the remainder is sequestered to bone for a prolonged period. Unabsorbed drug is eliminated unchanged in the faeces.

Absorption. Absorption of a single dose of risedronate was comparable when given 0.5 to 1 hour before breakfast or 2 hours after an evening meal in a study in healthy subjects.[1] The pharmacokinetics of risedronate are dose-proportional after a single oral dose.[2]

1. Mitchell DY, *et al.* The effect of dosing regimen on the pharmacokinetics of risedronate. *Br J Clin Pharmacol* 1999; 48: 536–42.
2. Mitchell DY, *et al.* Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. *J Clin Pharmacol* 2000; 40: 258–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actonel; Ductonar; Rentop; Ribastamin; Ridron; Risedon; *Austral.*: Acris; Actonel; Risedro; *Austria*: Actonel; *Belg.*: Actonel; *Braz.*: Actonel; Risedronel; Risedross; Risonato; *Canad.*: Actonel; *Chile*: Actonel; *China*: Gusong (???? (Sue Ho?)); Ji Wei (吉威); Wei Shan (唯善); *Cz.*: Actonel†; Juverital; Norifaz; Norsed†; Nurrid†; Rigat; Risendros; Tevanel; *Denm.*: Juverital; Nurrid; Optinate; Racidrix; Riseratio; Risostad: Vionate; *Fin.*: Optinate; Riseos†; Riseratio; Vionate†; *Fr.*: Actonel; *Ger.*: Actonel; *Gr.*: Actonel; Bondapen; Bonmate; Difosfon-S; Motivus; Riselib; *Hong Kong*: Actonel; *Hung.*: Actonel; Boneact; *India*: Actonel; Fossical; Gemfos; Risofos; *Indon.*: Actonel; Osteonate; Retonel; *Irl.*: Actonel; Ridate; Risonate; Risontel; *Israel*: Actonel; Ribone; *Ital.*: Actonel; Avestra; Optinate; *Jpn*: Actonel; Benet; *Malaysia*: Actonel; *Mex.*: Actonel; Alesone; Misodron; Reosvec; Seralis; Tecnodron; Teonav†; *Neth.*: Actonel; Melenor; Varibona; *Norw.*: Optinate; *Philipp.*: Actonel; *Pol.*: Actonel; Norifaz; Resorpate; Rigat; Risendros; *Port.*: Actonel; Norifaz; Norsed; Rizat; *Rus.*: Actonel (Актонель); Risendros (Рисендрос); *S.Afr.*: Actamax; Actonel; *Singapore*: Actonel; *Spain*: Actel; Actonel; Miosen; Risemyl†; *Swed.*: Optinate; *Switz.*: Actonel; *Thai.*: Actonel; *Turk.*: Actonel; Arilex; *UK*: Actonel; *Ukr.*: Risendros (Рисендрос)†; *USA*: Actonel; Atelvia; *Venez.*: Actonel.

Multi-ingredient Preparations. *Arg.*: Ribastamin Duo; Ridron Pack; *Austral.*: Actonel Combi D; Actonel Combi; *Belg.*: Actonel Combi D; *Canad.*: Actonel plus Calcium†; *Denm.*: Optinate Combi; *Fin.*: Optinate Combi D†; *Fr.*: Actonelcombi; *Ger.*: Actonel plus Calcium D; Actonel plus Calcium; *Hong Kong*: Actonel plus Calcium D; *Hung.*: Actonel Trio; Norifaz Trio *Irl.*: Actonel Combi; Actonel Plus Ca & D; *Mex.*: Actonel Trio; Seralis VIP; *Neth.*: ActoCalD†; Actokit D; Actokit; Actonel plus Calcium†; *Swed.*: Optinate Combi†; *UK*: Actonel Combi; *USA*: Actonel with Calcium†.

Pharmacopoeial Preparations
USP 36: Risedronate Sodium Tablets.

Strontium Ranelate *(rINNM)*

FK-481; Ranelate de Strontium; Ranelato de estroncio; S-12911; Strontii Ranelas; Стронций Ранелат.

2-(2-Carboxy-4-cyano-5-[*N*,*N*-di(carboxymethyl)amino]thiophen-3-yl) acetic acid distrontium salt.

$C_{12}H_6N_2O_8SSr_2$=513.5

CAS — 135459-87-9.

ATC — M05BX03.

ATC Vet — QM05BX03.

UNII — 04NQ160FRU (strontium ranelate); 8PD480E506 (strontium ranelate octahydrate).

Uses and Administration

Strontium ranelate is claimed to stimulate bone formation as well as reduce bone resorption. It is used to treat severe osteoporosis (below) in postmenopausal women at high risk of fracture and in men at increased risk of fracture. The recommended oral dose is 2 g daily, given at night and preferably at least 2 hours after food.

For details of administration in renal impairment, see below.

References.

1. Marie PJ. Strontium ranelate: new insights into its dual mode of action. *Bone* 2007; 40 (suppl 1): S5–S8.
2. Fonseca JE. Rebalancing bone turnover in favour of formation with strontium ranelate: implications for bone strength. *Rheumatology (Oxford)* 2008; 47 (suppl 4): iv17–iv19.

Administration in renal impairment. Strontium excretion occurs via the kidneys and clearance decreases as creatinine clearance (CC) decreases. UK licensed product information states that no dosage adjustment of strontium ranelate is required in patients with mild to moderate renal impairment (CC 30 to 70 mL/minute). However, it is not recommended for those with severe renal impairment (CC below 30 mL/minute) because of a lack of pharmacokinetic data in these patients; continuation of treatment in patients developing severe renal impairment should be considered on an individual basis.

Osteoporosis. Strontium ranelate, given orally with calcium and vitamin D supplements, has been found to reduce the risk of vertebral[1] and non-vertebral[2] fractures in postmenopausal women with osteoporosis (p. 1168.1). A pooled analysis of data from these 2 studies concluded that strontium ranelate reduced both vertebral and non-vertebral fractures in patients aged 80 years or older.[3] Protection against fractures was detected within 12 months, and sustained throughout 3 years of treatment. Hip fractures were also reduced over 3 years, but this did not reach statistical significance; the authors concluded that the analysis may not have been sufficiently powered in this respect. A systematic review[4] concluded that while strontium ranelate reduces vertebral fractures, there is less of a reduction with non-vertebral fractures, and the effect on hip fracture remains unclear. Some have cautioned about the interpretation of bone mineral density (BMD) changes with strontium ranelate, since stronger X-ray attenuation by strontium compared with calcium must be corrected for to avoid overestimating the effect. However, increases in BMD could be useful clinically in gauging long-term compliance.[5]

NICE considers strontium ranelate an alternative treatment option for both primary[6] and secondary[7] prevention of osteoporotic fragility fractures in high-risk postmenopausal women who are unable to take a bisphosphonate. A review[8] of the place of strontium ranelate in therapy considered that although it might be an alternative in patients who could not tolerate a bisphosphonate there was no convincing published evidence to support claims that it stimulated bone formation as well as reducing resorption. Further reviews[4,9] concluded that additional research to confirm its mechanism of action is required and that long-term fracture data are needed, along with comparative studies evaluating the efficacy of strontium ranelate relative to other therapies such as bisphosphonates. A subsequent review[10] reported that strontium ranelate reduced the risk of vertebral and nonvertebral fractures in two studies lasting 5 years and continued to provide protection against new fractures during the 3-year extensions of these studies.

Strontium ranelate has also been reported to have beneficial effects on measure of bone mineral density and markers of bone resorption in men with osteoporosis.[11]

1. Meunier PJ, *et al.* The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004; 350: 459–68.
2. Reginster JY, *et al.* Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005; 90: 2816–22.
3. Seeman E, *et al.* Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006; 21: 1113–20.
4. O'Donnell S, *et al.* Strontium ranelate for preventing and treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Fogelman I, Blake GM. Strontium ranelate for the treatment of osteoporosis: is useful, but changes in bone mineral density need careful interpretation. *BMJ* 2005; 330: 1400–1.
6. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women amended: Technology Appraisal 160 (issued January 2011). Available at: http://guidance.nice.org.uk/nicemedia/live/11746/47176/47176.pdf (accessed 24/06/13)
7. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women amended: Technology Appraisal 161 (issued January 2011). Available at: http://guidance.nice.org.uk/nicemedia/live/11748/42447/42447.pdf (accessed 24/06/13)
8. Anonymous. Strontium ranelate for osteoporosis? *Drug Ther Bull* 2006; 44: 29–32.
9. Stevenson M, *et al.* The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007; 11: 1–134.
10. Deeks ED, Dhillon S. Strontium ranelate: a review of its use in the treatment of postmenopausal osteoporosis. *Drugs* 2010; 70: 733–59.
11. Kaufman JM, *et al.* Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. *J Clin Endocrinol Metab* 2013; 98: 592–601.

Adverse Effects and Precautions

Common adverse effects of strontium ranelate include gastrointestinal disturbances, headache, dermatitis, and eczema. Disturbances in consciousness, memory loss, and seizures may occur and there have been reports of alopecia, pyrexia, confusion, peripheral oedema, and bronchial hyperreactivity.

Treatment with strontium ranelate has been associated with an increased incidence in venous thromboembolism including pulmonary embolism, and its use is contra-indicated in patients considered at risk or with a history of thromboembolic disorders. A higher risk of myocardial infarction has also been reported, and the use of strontium ranelate is contra-indicated in patients with a history of ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, or uncontrolled hypertension. It should be used with caution in patients with other significant risk factors for cardiovascular events. Transient reversible increases in creatine kinase activity have been reported. Hypersensitivity reactions, including rash, pruritus, urticaria, angioedema, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred. Drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, has also been reported.

Strontium may interfere with certain methods used for the determination of serum and urinary calcium.

Strontium ranelate should not be given with food or antacids—see Interactions, below.

Alopecia. Between May 2005 and January 2008, the Spanish pharmacovigilance system received 5 reports of alopecia associated with strontium ranelate treatment.[1] A causal association was suspected due to the temporal relationship between the start of treatment and the onset of alopecia, the improvement of most cases on drug withdrawal, and the exclusion of other causes. Inorganic strontium has also traditionally been a component of depilatory creams. One of the reported cases also had some features of Stevens-Johnson syndrome, and the authors suggested that alopecia may be one symptom of a more complex and severe hypersensitivity syndrome.

1. Sainz M, *et al.* Strontium ranelate may cause alopecia. *BMJ* 2009; 338: b1494.

Effects on the cardiovascular system. In a cohort analysis of strontium ranelate used in general practice, mainly for postmenopausal osteoporosis, there was a crude annual incidence of venous thromboembolism of 6.24 cases per 1000 patient-years exposed. This was similar to estimates in populations of similar age and in populations treated for osteoporosis. However, a history of venous thromboembolism was identified as a significant risk factor.[1]

1. Osborne V, *et al.* Incidence of venous thromboembolism in users of strontium ranelate: an analysis of data from a prescription-event monitoring study in England. *Drug Safety* 2010; 33: 579–91.

Hypersensitivity. As of November 2007, the EMEA had received reports of 16 cases of drug rash with eosinophilia and systemic symptoms (DRESS), a serious and life-threatening condition, in patients treated with strontium ranelate. Two fatalities were reported. Reactions appeared within 3 to 6 weeks of starting therapy, with skin rash, accompanied by fever, swollen glands, eosinophilia, and effects on the liver, kidneys, and lungs. Patients are advised to stop treatment with strontium ranelate if a rash occurs and to seek medical advice; treatment should not be restarted.[1] Similar advice, and a reminder that the drug should also be used with caution in patients with risk factors for venous thromboembolism, was issued in June 2008 by the Australian regulatory authorities; although there had been no fatalities, they had seen 16 reports of rash, one accompanied by fever and one by eosinophilia.[2]

1. EMEA. EMEA recommends changes in the product information for Protelos/Osseor due to the risk of severe hypersensitivity reactions (issued 16th November 2007). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease_Protelos_41745807en.pdf (accessed 21/01/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Severe skin reactions and venous thromboembolism with strontium ranelate (Protos). *Aust Adverse Drug React Bull* 2008; 27: 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0806.pdf (accessed 17/07/08)

Interactions

Food, milk, and calcium-containing compounds may reduce the bioavailability of strontium ranelate; antacids containing aluminium or magnesium may reduce its absorption. Such products should be given at least 2 hours apart from, and, in the case of antacids, preferably after, strontium ranelate. Because of possible complex formation, strontium ranelate should not be given with oral tetracyclines or quinolones.

Pharmacokinetics

Strontium ranelate has an absolute bioavailability of about 25% after an oral dose; calcium or food reduces the bioavailability by about 60 to 70%. Peak plasma concentrations are achieved 3 to 5 hours after an oral dose. Plasma protein binding is low. Strontium ranelate has a high affinity for bone tissue. It is not metabolised, and has a half-life of about 60 hours. Excretion occurs via the kidneys and gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Osteovital: Prodinam; Protos; Troncel; *Austral.*: Protos; *Austria*: Protelos; *Belg.*: Protelos; *Braz.*: Protos; *Chile*: Protelos; *China*: Osseor (欧思美); *Cz.*: Osseor; Protelos; *Denm.*: Protelos; *Fr.*: Protelos; *Ger.*: Protelos; *Gr.*: Protelos; *Hong Kong*: Protos; *Hung.*: Protelos; *Indon.*: Protos; *Irl.*: Osseor; Protelos; *Israel*: Protelos; *Ital.*: Osseor; Protelos; *Malaysia*: Protaxos; *Neth.*: Osseor; Protelos; *NZ*: Protos; *Philipp.*: Protos; *Pol.*: Osseor; Protelos; *Port.*: Osseor; Protelos; *Rus.*: Bivalos (Бивалос); *S.Afr.*: Protos; *Singapore*: Protos; *Spain*: Osseor; Protelos; *Swed.*: Protelos; *Thai.*: Protaxos; *Turk.*: Protelos; *UK*: Protelos; *Ukr.*: Bivalos (Бивалос).

Multi-ingredient Preparations. *Arg.*: Osteovital Plus.

Teriparatide *(BAN, USAN, rINN)*

(1-34) Human parathormone; (1-34) Human parathyroid hormone; 1-34 Parathormone (human); hPTH 1-34; Human parathormone (1-34); Human parathyroid hormone (1-34); Human PTH (1-34); LY-333334; Parathyroid hormone peptide (1-34); Teriparatid; Teriparatida; Tériparatide; Teriparatidum; Терипаратид.

$C_{181}H_{291}N_{55}O_{51}S_2$=4117.8

CAS — 52232-67-4.

ATC — H05AA02.

ATC Vet — QH05AA02.

UNII — 10T9CSU89I.

Teriparatide Acetate *(BANM, USAN, rINNM)*

Acetato de teriparatida; Teriparatida, acetato de; Tériparatide, Acétate de; Teriparatidi Acetas; Терипаратида Ацетат.

$C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.yC_2H_4O_2$

CAS — 99294-94-7 (teriparatide acetate).

ATC — H05AA02.

ATC Vet — QH05AA02.

UNII — 9959P4V12N.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid biologically active N-terminal region of human parathyroid hormone (p. 1188.3). It is used in the treatment of established postmenopausal osteoporosis, especially in those with a high fracture risk, and in men with primary or hypogonadal osteoporosis who are at increased risk of fracture. Teriparatide may also be used to treat osteoporosis associated with prolonged corticosteroid therapy in women and men at increased risk of fracture.

The usual dose of teriparatide is 20 micrograms subcutaneously daily into the thigh or abdominal wall. Treatment is limited to a maximum of 2 years in total. A transdermal formulation is also under investigation.

Teriparatide acetate has been given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism. Hypoparathyroidism is characterised by a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism is characterised by resistance to the effects of parathyroid hormone (see p. 1171.2). Teriparatide acetate is used *diagnostically* to distinguish between these 2 conditions.[1] A synthetic 1-38 fragment of human parathyroid hormone (hPTH 1-38) has been used similarly.[2] Teriparatide has also been used to *treat* hypoparathyroidism.[3-5]

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; 109: 800–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; 146: 373–7.
3. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* 1996; 276: 631–6.
4. Winer KK, *et al.* A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998; 83: 3480–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; 88: 4214–20.

Osteoporosis. Parathyroid hormone is capable of stimulating both formation and resorption of bone. Continuous infusion of teriparatide leads to a persistent elevation of parathyroid hormone and greater bone resorption by stimulating osteoclasts, with a net decrease in bone volume, and resultant hypercalcaemia; in contrast, daily (intermittent) injections increase bone volume by increasing osteoblastic proliferation.[1-3] Teriparatide appears to have less effect on cortical than trabecular bone,[3] suggesting that, although it may be helpful in preventing vertebral fractures, its impact on fractures of the proximal femur may be more limited. However, while treatment with teriparatide substantially increases lumbar spine bone mineral density (BMD), beneficial increases are also seen at the hip,[1] and in a pivotal study (the Fracture Prevention Trial)[4] in **postmenopausal** women with osteoporosis (p. 1168.1), it decreased the risk of both vertebral and non-vertebral fracture. In a follow-up study, the reduction in vertebral fracture risk in patients treated with teriparatide for a mean of 19 months persisted for at least an additional 18 months after daily treatment was stopped.[5] Teriparatide appears to improve bone geometry, with no detrimental effect on cortical bone.[6] In the UK, NICE[7] recommends teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women who have had an unsatisfactory response to bisphosphonates or who are unable to take bisphosphonates or strontium ranelate; women aged 65 years or older must have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3.5 standard deviations or more below the mean) plus more than 2 fractures, and women aged 55 to 64 should have an extremely low BMD plus more than 2 fractures. It has been pointed out that evidence of reduction in teriparatide's effect with current or recent alendronate therapy (see below) might make its use as a second-line agent problematic.[8]

Data on combination therapy are limited, but some studies suggest that teriparatide with HRT is more effective than HRT alone.[9] Previous HRT treatment, however, may attenuate the BMD increases seen with teriparatide alone.[10] Increases in BMD have been reported in patients taking teriparatide with or after raloxifene.[10] The effect of teriparatide with the antiresorptive bisphosphonates has yet to be determined.[2,6,9,11] Although there is some suggestion that teriparatide still increases bone formation after treatment with alendronate,[9] a study in men found that, when given together, alendronate impaired the anabolic effects of teriparatide.[12] For this reason, some consider that teriparatide be started immediately after stopping bisphosphonates.[11]

It has been suggested that the degree of suppression of bone turnover before treatment[6] or the bisphosphonate used previously[13] may influence the response to teriparatide. A study of daily or cyclical teriparatide in women with osteoporosis found that although the teriparatide-induced increase in BMD may be slightly lower in women who had previously taken alendronate than in those who had never received it, the increase in spinal BMD was still impressive. Intermittent cyclical treatment with teriparatide had similar effects on BMD to daily dosage.[14] Bisphosphonate therapy has been recommended to maintain BMD improvements after teriparatide treatment.[10]

In postmenopausal women with osteoporosis taking HRT and **corticosteroids,**[15] the addition of teriparatide significantly increased BMD of the lumbar spine; modest changes in hip bone mass were not significant.

In men with osteoporosis, teriparatide increased BMD in the lumbar spine and at the femoral neck;[9] risk of fracture was also reduced.[1]

1. Cappuzzo KA, Delafuente JC. Teriparatide for severe osteoporosis. *Ann Pharmacother* 2004; 38: 294–302.
2. Madore GR, *et al.* Parathyroid hormone. *J Am Acad Orthop Surg* 2004; 12: 67–71.
3. Brixen KT, *et al.* Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. *Basic Clin Pharmacol Toxicol* 2004; 94: 260–70.
4. Neer RM, *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344: 1434–41.
5. Lindsay R, *et al.* Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med* 2004; 164: 2024–30.
6. Rubin MR, Bilezikian JP. Parathyroid hormone as an anabolic skeletal therapy. *Drugs* 2005; 65: 2481–98.
7. NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 161 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA161guidance.pdf (accessed 12/01/09)
8. Anonymous. Teriparatide for postmenopausal osteoporosis. *Drug Ther Bull* 2004; 42: 93–5.
9. Quattrocchi E, Kourlas H. Teriparatide: a review. *Clin Ther* 2004; 26: 841–54.
10. Stroup J, *et al.* Teriparatide in the treatment of osteoporosis. *Am J Health-Syst Pharm* 2008; 65: 532–9.
11. Deal C. The use of intermittent human parathyroid hormone as a treatment for osteoporosis. *Curr Rheumatol Rep* 2004; 6: 49–58.
12. Pinkelstein JS, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; 349: 1216–26.
13. Miller PD, *et al.* Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J Clin Endocrinol Metab* 2008; 93: 3785–93.
14. Cosman F, *et al.* Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; 353: 566–75.
15. Lane NE, *et al.* Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. *J Clin Invest* 1998; 102: 1627–33.

Adverse Effects and Precautions

Gastrointestinal disturbances, pain in the limb of injection, headache, and dizziness are the most common adverse effects in patients treated with subcutaneous teriparatide. Dizziness, vertigo, and syncope may be associated with transient orthostatic hypotension in some patients, particularly when beginning treatment. Those so affected should not drive or operate potentially hazardous machinery. Asthenia, arthralgia, anaemia, tachycardia, emphysema, and rhinitis may occur. Angina pectoris, depression, dyspnoea, leg cramps, pneumonia, urinary disorders, and sciatica have also been reported. Muscle spasms have been commonly reported, sometimes after the first dose; serious back spasms may occur very rarely. A metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate. It is a peptide and the possibility of systemic hypersensitivity reactions should be borne in mind. Renal impairment has been reported. Hypercalcaemia may develop with teriparatide or the acetate and it is therefore contra-indicated in patients with pre-existing hypercalcaemia. Transient increases in serum calcium concentrations have been noted after teriparatide injection in normocalcaemic patients; any blood monitoring should be carried out at least 16 hours after the most recent dose. Hypercholesterolaemia and hyperuricaemia have also been reported. Caution is advised in patients with active or recent renal calculi.

Teriparatide is contra-indicated in patients with severe renal impairment and should be used with caution with those with moderate impairment. Teriparatide is also contra-indicated in pregnancy as studies in *animals* have shown reproductive toxicity.

There was an increased incidence of osteosarcoma in *rats* and rare reports in humans given teriparatide; it should not be used in patients who may be at increased risk, including those with a history of skeletal metastases or previous radiotherapy to the skeleton, those with metabolic bone disease such as Paget's disease and hyperparathyroidism, those with unexplained elevations of serum alkaline phosphatase, or children and young adults with open epiphyses.

Pharmacokinetics

Teriparatide is extensively absorbed after subcutaneous injection; peak plasma concentrations are reached after about 30 minutes. Absolute bioavailability is reported to be about 95%. The serum half-life is 5 minutes after intravenous use, and approximately 1 hour after subcutaneous injection (reflecting time needed for absorption from the injection site). No studies have been done on the metabolism or excretion of teriparatide; parathyroid hormone is believed to be enzymatically metabolised in the liver and excreted by the kidneys.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Forteo; *Austral.*: Forteo; *Austria*: Forsteo; *Belg.*: Forsteo; *Braz.*: Forteo; *Canad.*: Forteo; *Chile*: Forteo; *China*: Forsteo (复泰奥); *Cz.*: Forsteo; *Denm.*: Forsteo; *Fin.*: Forsteo; *Fr.*: Forsteo; *Ger.*: Forsteo; *Gr.*: Forsteo; *Hong Kong*: Forteo; *Hung.*: Forsteo; *India*: Forteo; *Irl.*: Forsteo; *Israel*: Forteo; *Ital.*: Forsteo; *Jpn*: Teribone; *Malaysia*: Forteo; *Mex.*: Forteo; *Neth.*: Forsteo; *Norw.*: Forsteo; *NZ*: Forteo; *Philipp.*: Forteo; *Pol.*: Forsteo; *Port.*: Forsteo; *Rus.*: Forsteo (Форстео); *S.Afr.*: Forteo; *Singapore*: Forteo; *Spain*: Forsteo; *Swed.*: Forsteo; *Switz.*: Forsteo; *Thai.*: Forteo; *Turk.*: Forsteo; *UK*: Forsteo; *USA*: Forteo; *Venez.*: Forteo.

Tiludronate

ATC — M05BA05.
ATC Vet — QM05BA05.

Tiludronic Acid *(BAN, rINN)*

Acide Tiludronique; Ácido tiludrónico; Acidum Tiludronicum; ME-3737; SR-41319; Tiludrónico, ácido; Tiludronihappo; Tiludronik Asit; Tiludronsyra; Тилудроновая Кислота.
{[(*p*-Chlorophenyl)thio]methylene}diphosphonic acid.
$C_7H_9ClO_6P_2S$=318.6
CAS — 89987-06-4.
ATC — M05BA05.
ATC Vet — QM05BA05.
UNII — 6PNS59HP4Y.

Tiludronate Disodium *(USAN)*

Disodium Tiludronate; Natrii Tiludronas; Sodium Tiludronate; SR-41319B; Tiludronate de Sodium; Tiludronate Sodium (BANM); Tiludronato sódico; Tiludronato sódico; Натрий Тилудронат.
Disodium dihydrogen {[(*p*-chlorophenyl)thio]methylene} diphosphonate hemihydrate.
$C_7H_7ClNa_2O_6P_2S,½H_2O$=371.6
CAS — 149845-07-8 (anhydrous disodium tiludronate); 155453-10-4 (tiludronate disodium hemihydrate).
ATC — M05BA05.
ATC Vet — QM05BA05.
UNII — BH6M93CIA0.

Uses and Administration

Tiludronate is a bisphosphonate with similar properties to those of the bisphosphonates in general (p. 1173.3). It inhibits bone resorption and is used for Paget's disease of bone.

It is given orally as tiludronate disodium, but doses are expressed in terms of the equivalent amount of tiludronic acid; 117 mg of tiludronate disodium is equivalent to about 100 mg of tiludronic acid. To ensure adequate absorption doses should be taken with plenty of water (at least 200 mL), at least 2 hours before or after meals. In Paget's disease of bone the usual dose is 400 mg once daily for 3 months, and this may be repeated if necessary after an interval of at least 3 to 6 months.

Tiludronate has been tried in postmenopausal osteoporosis, but results were disappointing.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including tiludronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p. 1174.3. Asthenia and dizziness have been reported rarely.

Carcinogenicity. Oesophageal cancer has been reported in patients who had taken oral bisphosphonates, see Carcinogenicity, under Bisphosphonates, p. 1175.2.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including tiludronate, see under Bisphosphonates, p. 1176.1.

Effects on the musculoskeletal system. Atypical fractures and osteonecrosis of the jaw have been reported after the use of bisphosphonates, see under Adverse Effects of Bisphosphonates, p. 1176.2 and p. 1176.3, respectively.

Effects on the skin. As with other bisphosphonates, tiludronate has been associated with rash and pruritus. For reference to a case of massive epidermal necrosis possibly associated with tiludronate, see Hypersensitivity, under Bisphosphonates, p. 1177.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tiludronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2. Indometacin may increase the bioavailability of tiludronate two to fourfold; diclofenac does not appear to have this effect. Aspirin may decrease the bioavailability of tiludronate by 50%.

Pharmacokinetics

Like other bisphosphonates tiludronate is poorly absorbed after oral doses. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The oral bioavailability of tiludronate is about 6% in the fasting state, and is reduced by about 90% when given within 2 hours of food. Plasma protein binding is about 90%, mostly to albumin. Tiludronate is not metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Skelid; *Belg.*: Skelid; *Fr.*: Skelid; *Ger.*: Skelid†; *Hung.*: Skelid†; *Neth.*: Skelid†; *Port.*: Skelid†; *Spain*: Skelid; *Switz.*: Skelid†; *UK*: Skelid†; *USA*: Skelid.

Zoledronate

ATC — M05BA08.
ATC Vet — QM05BA08.

Zoledronic Acid *(BAN, USAN, rINN)*

Acide Zolédronique; Ácido zoledrónico; Acidum Zoledronicum; CGP-42446; Tsoledronihappo; Zoledrónico, ácido; Zoledronik Asit; Zoledronsyra; Золедроновая Кислота.
(1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid.
$C_5H_{10}N_2O_7P_2$=272.1
CAS — 118072-93-8 (anhydrous zoledronic acid); 165800-06-6 (zoledronic acid monohydrate).
ATC — M05BA08.
ATC Vet — QM05BA08.
UNII — 70HZ18PH24 (anhydrous zoledronic acid); 6XC1PAD3KF (zoledronic acid monohydrate).

Incompatibility. Zoledronic acid should not be mixed with calcium or other infusion solutions such as lactated Ringer's solution that contain divalent cations.

Stability. Zoledronic acid infusion is physically stable for 24 hours at 2 degrees to 8 degrees once diluted to 100 mL in sodium chloride 0.9% or glucose 5% as per licensed product information.

Zoledronate Disodium *(BANM, USAN, rINNM)*

CGP-42446A; ZOL-446; Zoledronas Dinatricum; Zolédronate Disodique; Zoledronato disódico; Динатрий Золедронат.
Disodium dihydrogen (1-hydroxy-2-imidazol-1-ylethylidene) diphosphonate tetrahydrate.
$C_5H_8N_2Na_2O_7P_2,4H_2O$=388.1
CAS — 165800-07-7.
ATC — M05BA08.
ATC Vet — QM05BA08.
UNII — 7D7GS1SA24.

Zoledronate Trisodium *(BANM, USAN, rINNM)*

CGP-42446B; Zoledronas Trinatricum; Zolédronate Trisodique; Zoledronato trisódico; Тринатрий Золедронат.
Trisodium hydrogen (1-hydroxy-2-imidazol-1-ylethylidene) diphosphonate hydrate (5:2).
$C_5H_7N_2Na_3O_7P_2,2½H_2O$=383.1
CAS — 165800-08-8.
ATC — M05BA08.
ATC Vet — QM05BA08.
UNII — ARL915IH66.

Uses and Administration

Zoledronate is an aminobisphosphonate (p. 1173.3) that is a potent inhibitor of bone resorption. It is used for the treatment of hypercalcaemia of malignancy, and Paget's disease of bone, as well as for prevention of skeletal events in patients with advanced bone malignancies. It is also used for the treatment and prevention of glucocorticoid-induced osteoporosis and osteoporosis in postmenopausal women.

and for the treatment of osteoporosis in men. Zoledronic acid is given as an intravenous infusion over not less than 15 minutes.

For **hypercalcaemia of malignancy** a single dose of 4 mg is used, diluted with 100 mL of sodium chloride 0.9% or glucose 5%. The treatment may be repeated if necessary after at least 7 days, at a dose of 4 mg. Individual doses should not exceed 4 mg, as there is an increased risk of adverse renal effects, including renal failure.

Zoledronic acid is given for the prevention of skeletal events in patients with advanced **bone malignancies** (p. 700.3) at a dose of 4 mg, diluted as above, every 3 to 4 weeks.

For the treatment of **Paget's disease** of bone, zoledronic acid is given as a single intravenous infusion of 5 mg. Patients who relapse can be re-treated with zoledronic acid; an additional intravenous infusion of 5 mg may be given after an interval of at least 1 year from the initial dose.

For the treatment of postmenopausal **osteoporosis**, osteoporosis in men, and glucocorticoid-induced osteoporosis, the recommended dose is a single intravenous infusion of zoledronic acid 5 mg given once a year. In patients with a recent low-trauma hip fracture, it is recommended that zoledronic acid should be started 2 or more weeks after hip fracture repair. In the USA, the same dose is also given annually for the prevention of glucocorticoid-induced osteoporosis; for the prevention of postmenopausal osteoporosis, a single dose of 5 mg zoledronic acid is given once every 2 years.

For doses in renal impairment, see below.

Calcium and vitamin D supplements are recommended for patients with advanced bone malignancies, Paget's disease, and osteoporosis treated with zoledronic acid.

Reviews.

1. Cheer SM, Noble S. Zoledronic acid. *Drugs* 2001; 61: 799–805.
2. Theriault RL. Zoledronic acid (Zometa) use in bone disease. *Expert Rev Anticancer Ther* 2003; 3: 157–66.
3. Neville-Webbe H, Coleman RE. The use of zoledronic acid in the management of metastatic bone disease and hypercalcaemia. *Palliat Med* 2003; 17: 539–53.
4. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther* 2003; 25: 2669–2708.
5. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; 63: 417–37.
6. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; 64: 1197–1211.
7. Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. *Cancer Treat Rev* 2008; 34: 183–92.
8. Lyseng-Williamson KA. Zoledronic acid: a review of its use in breast cancer. *Drugs* 2008; 68: 2661–82.
9. Anonymous. Annual zoledronic acid for osteoporosis. *Drug Ther Bull* 2008; 46: 93–6.

Administration in renal impairment. Despite the fact that renal clearance of zoledronic acid correlates to renal function, a pharmacokinetic study[1] concluded that no dosage adjustment appeared necessary in patients with mild to moderate renal impairment (creatinine clearance 50 to 80 mL/minute, and 10 to 50 mL/minute, respectively).

Licensed product information also states that no adjustment is necessary in mild to moderate renal impairment for patients with **hypercalcaemia of malignancy**, but defines this degree of impairment in terms of serum creatinine less than 400 micromoles/litre or less than 4.5 mg per 100 mL; the risks and benefits of therapy should be considered before treating those with more severe impairment.

However, for patients with advanced **bone malignancies**, the intravenous dose of zoledronic acid should be adjusted on the basis of creatinine clearance (CC) as follows:

- CC greater than 60 mL/minute: 4 mg (no adjustment necessary)
- CC 50 to 60 mL/minute: 3.5 mg
- CC 40 to 49 mL/minute: 3.3 mg
- CC 30 to 39 mL/minute: 3 mg
- CC below 30 mL/minute: treatment not recommended

Serum creatinine should be measured before each dose and treatment withheld if renal function has deteriorated. Renal deterioration is defined as an increase of 44 micromoles/litre or 500 micrograms per 100 mL for those patients with normal baseline creatinine, and an increase of 88 micromoles/litre or 1 mg per 100 mL for those with abnormal baseline creatinine. Treatment may be restarted at the dose used before treatment interruption once the creatinine returns to within 10% of the baseline value.

For patients with **Paget's disease** or **osteoporosis**, licensed product information states that no dose adjustment is considered necessary for those with CC of 35 mL/minute or more; treatment is contra-indicated in those with CC of less than 35 mL/minute or evidence of acute renal impairment due to an increased risk of renal failure.

1. Skerjanec A, *et al.* The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003; 43: 154–62.

Charcot neuroarthropathy. Bisphosphonates, including zoledronic acid, have been tried for Charcot neuroarthropathy, see under Bisphosphonates, p. 1174.1.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p. 1167.2) once the patient has been adequately rehydrated. Zoledronate has been shown to have a faster onset, higher response rate, and longer duration of action than pamidronate.[1] It also has a shorter infusion time than pamidronate,[1] and some consider it the treatment of choice for hypercalcaemia of malignancy.[2-4] However, zoledronate has caused severe hypocalcaemia in some patients, see Effects on Electrolytes, below.

1. Major P, *et al.* Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; 19: 558–67.
2. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. *Oncologist* 2002; 7: 481–91.
3. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; 63: 417–37.
4. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; 64: 1197–1211.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p. 700.3) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Zoledronate is licensed for such use in many countries.[1]

In the treatment of skeletal complications from bone metastases secondary to multiple myeloma or breast cancer, zoledronate was more effective than pamidronate in reducing the risk of complications from breast cancer; it was of similar efficacy in those with multiple myeloma.[2] In a placebo-controlled study in patients with prostate cancer,[3] zoledronate reduced the number of skeletal-related events, and increased the median time to events. In patients with bone metastases arising from lung cancer and other solid tumours (excluding breast or prostate cancer), zoledronate reduced skeletal morbidity; the primary end-point, which excluded hypercalcaemia as a skeletal-related event, did not reach statistical significance.[4] However, the authors noted that the patient groups had a shorter-than-expected survival-time. A longer term follow-up of this study[5] confirmed a sustained reduction in risk of developing skeletal events with zoledronate. A later meta-analysis[6] confirmed the benefits of the bisphosphonate in reducing skeletal events, and hence morbidity, in patients with cancer, but not mortality; however, no clear advantage could be shown versus clodronate or pamidronate, which were also of benefit. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear. For the suggestion that zoledronate may have wider benefits against non-skeletal malignancy, see below.

1. Dhillon S, Lyseng-Williamson KA. Zoledronic Acid: a review of its use in the management of bone metastases of malignancy. *Drugs* 2008; 68: 507–34.
2. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003; 98: 1735–44.
3. Saad F, *et al.* Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004; 96: 879–82.
4. Rosen LS, *et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003; 21: 3150–7.
5. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer* 2004; 100: 2613–21.
6. Machado M, *et al.* Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009; 31: 962–79.

Malignant neoplasms of the breast. For the suggestion that bisphosphonates, including zoledronate, may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

Multiple myeloma. For the effect of bisphosphonates, including zoledronic acid, on survival in multiple myeloma, see under Bisphosphonates, p. 1174.2.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p. 1168.1). Five different dosage regimens of zoledronate all increased bone mineral density (BMD) in **postmenopausal** women when given intermittently over the course of 1 year in a placebo-controlled study.[1] Compared with placebo, a once-yearly infusion of zoledronate over a 3-year period significantly reduced the risk of vertebral, hip, and other fractures in postmenopausal women with osteoporosis.[2] BMD was also significantly increased. Adverse events were similar in both groups, including renal function changes; however, serious atrial fibrillation occurred more frequently in the zoledronate group (see Effects on the Heart, under Bisphosphonates, p. 1175.3). Once-yearly infusion of zoledronate beginning within 90 days after surgical repair of a low-trauma hip fracture was associated with a reduction in the rate of new vertebral and non-vertebral fractures, although the reduction in the risk of new hip fractures was non-significant.[3] Further studies comparing once-yearly zoledronic acid with oral bisphosphonates are needed to determine their place in the management of osteoporosis.[4] The use of zoledronate for osteoporosis in men has also been reviewed.[5]

An integrated analysis of interim (12 month) results from 2 studies evaluating zoledronate for the prevention of cancer **treatment-induced** bone loss, in postmenopausal women with early breast cancer treated with letrozole, suggested that adding zoledronate to the regimen from the start was more effective than delaying treatment until there was evidence of bone loss.[6] Zoledronic acid has also been shown to prevent bone loss in premenopausal women undergoing chemotherapy for early breast cancer.[7,8]

In a small study,[9] zoledronate improved the calcium content of cancellous bone, maintained femoral neck BMD, and increased lumbar spine BMD after kidney transplantation. In a similar study of liver transplant recipients, zoledronate also had favourable effects on BMD. This effect tended to diminish at 12 months when compared with placebo; the authors considered this to be due to improved general health, mobility, muscle mass, and nutrition as a consequence of improved liver function.[10]

1. Reid IR, *et al.* Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002; 346: 653–61.
2. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; 356: 1809–22.
3. Lyles KW, *et al.* HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357: 1799–1809.
4. Woodis CB. Once-yearly administered intravenous zoledronic acid for postmenopausal osteoporosis. *Ann Pharmacother* 2008; 42: 1085–9.
5. Maricic M. Intravenous zoledronic acid: what are the indications for male osteoporosis? *Curr Osteoporos Rep* 2010; 8: 4–9.
6. Brufsky A, *et al.* Z-FAST and ZO-FAST Study Groups. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008; 13: 503–14.
7. Hershman DL, *et al.* Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2008; 26: 4739–45.
8. Gnant M, *et al.* Austrian Breast and Colorectal Cancer Study Group (ABCSG). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol* 2008; 9: 840–9.
9. Haas M, *et al.* Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 2003; 63: 1130–6.
10. Crawford BAL, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; 144: 239–48.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p. 1169.3) if bone pain is persistent, or to prevent further progression of the disease. Zoledronate is highly effective in Paget's disease. Single infusions of up to 400 micrograms have been shown to inhibit bone resorption in patients with active Paget's disease.[1,2] In a patient[3] with disease refractory to other bisphosphonates, a single infusion of 4 mg improved symptoms and improved biochemical markers of disease activity. A placebo-controlled study compared a single infusion of 5 mg zoledronic acid with a 60-day course of oral risedronate 30 mg daily. Patients receiving zoledronic acid had significantly more rapid and marked reduction in serum alkaline phosphatase concentrations, higher response rates, and shorter median times to response than those on risedronate. During an open extension study, patients on risedronate had a significantly larger loss of therapeutic response than those given zoledronic acid.[4] A review[5] concluded that zoledronic acid was an important first-line treatment for Paget's disease.

1. Arden-Cordone M, *et al.* Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int* 1997; 60: 415–18.
2. Buckler H, *et al.* Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone* 1999; 24 (suppl): 81S–85S.
3. Chung G, Keen RW. Zoledronate treatment in active Paget's disease. *Ann Rheum Dis* 2003; 62: 275–6.
4. Reid IR, *et al.* Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005; 353: 898–908.
5. Keating GM, Scott LJ. Zoledronic acid: a review of its use in the treatment of Paget's disease of bone. *Drugs* 2007; 67: 793–804.

Adverse Effects and Precautions

As for the bisphosphonates in general, p. 1174.3.

Other adverse effects that have been reported with zoledronic acid include alopecia and hyperhidrosis.

Effect on electrolytes. Zoledronate has more potent effects on calcium than some of the other bisphosphonates, and has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in some patients.[1,2] In most cases, pre-existing conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1] Vit-

amin D deficiency should be treated before starting zoledronate.[1,2]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; 328: 335–6.
2. Breen TL, Shane E. Prolonged hypocalcemia after treatment with zoledronic acid in a patient with prostate cancer and vitamin D deficiency. *J Clin Oncol* 2004; 22: 1531–2.

Effects on the eyes. For reports of ocular effects with bisphosphonates, including zoledronate, see p. 1175.2.

Effects on the heart. For discussion of a possible increased risk of serious atrial fibrillation with bisphosphonates, including zoledronate, see Effects on the Heart, under Bisphosphonates, p. 1175.3.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, see under Bisphosphonates, p. 1176.1. It is important to ensure adequate hydration before and after doses of zoledronic acid as dehydration predisposes to deterioration in renal function. Treatment may need to be modified in some patients with renal impairment (see Administration in Renal Impairment, p. 1193.1).

Effects on the musculoskeletal system. Musculoskeletal reactions, atypical fractures, and osteonecrosis of the jaw have been reported after the use of bisphosphonates, including zoledronate, see under Adverse Effects of Bisphosphonates, p. 1176.2 *et seq.*

Effects on the nervous system. Seizures have been reported after intravenous infusion of zoledronic acid.[1]

1. Tsourdi E, *et al.* Seizures associated with zoledronic acid for osteoporosis. *J Clin Endocrinol Metab* 2011; 96: 1955–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zoledronate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for the bisphosphonates in general, p. 1177.2.

Pharmacokinetics

Plasma concentrations of zoledronate rise rapidly after the start of an intravenous infusion. Plasma protein binding is low; it has been reported to range between 28 and 56%. Zoledronate is not metabolised, and about 23 to 55% of the dose is excreted in the urine unchanged within 24 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Terminal elimination half-life is about 146 hours. Renal clearance is slower in patients with severe renal impairment (see Administration in Renal Impairment, p. 1193.1).

References.

1. Chen T, *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; 42: 1228–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aclasta; Dreico; Eriopl os; Ledron; Rionit; Simpla; Sinresor; Varidronico; Xedron†; Zo.ieta; ***Austral.***: Aclasta; Zometa; ***Austria***: Aclasta; Zometa; ***Belg.***: Aclasta; Zometa; ***Braz.***: Aclasta; Blaztere; Zometa; ***Can.d.***: Aclasta; Zometa; ***Chile***: Aclasta; Zometa; ***China***: Aclasta (必固达); Ai Lang (艾朗); Bo Lai Ning (博来宁); Gai Ning (盖柠); Su Qi (苏奇); Yin Li Da (因力达); YiTai (依泰); Zhen Da (晨达); Zhuo Lai (卓莱); Zometa (择泰); Zuorui (佐锐); Cz.: Aclasta; Zometa; ***Denm.***: Aclasta; Zometa; ***Fin.***: Aclasta; Zometa; ***Fr.***: Aclasta; Zometa; ***Ger.***: Aclasta; Zometa; ***Gr.***: Aclasta; Zometa; ***Hong Kong***: Aclasta; Zometa; ***Hung.***: Aclasta; Zometa; ***India***: Blaztere; Cytozol; Zoldria; Zometa; ***Indon.***: Aclasta; Zometa; ***Irl.***: Aclasta; Zometa; ***Israel***: Aclasta; Zometa; ***Ital.***: Aclasta; Zometa; ***Jpn***: Zometa; ***Malaysia***: Aclasta; Zometa; ***Mex.***: Zometa; ***Neth.***: Aclasta; Desinobon; Fayton; Symblasta; Zacidate; Zalit; Zoledreenos; Zolenia; Zometa; ***Norw.***: Aclasta; Zometa; ***NZ***: Aclasta; Zometa; ***Philipp.***: Aclasta; Zometa: ***Pol.***: Aclasta; Zometa; ***Port.***: Aclasta; Zometa; ***Rus.***: Aclasta (Акласта); Blaztere (Блаттера); Resorba (Резорба); Rezoklastin (Резокластин); Veroklast (Верокласт); Zolerix (Золерикс); Zometa (Зомета); ***S. Afr.***: Aclasta; Zobone; Zomedron; Zometa; ***Singapore***: Aclasta; Zometa; ***Spain***: Aclasta; Zometa; ***Swed.***: Aclasta; Zometa; ***Switz.***: Aclasta; Zolacin; Zometa; ***Thai.***: Aclasta; Leuzotev; Z nvel; Zolennic; Zometa; ***Turk.***: Aclasta; Ostezolen; Zoledrin; Zolenat; Zomebon; Zometa; ***UK***: Aclasta; Zometa; ***Ukr.***: Aclasta (Акласта); Blazter (Блазтер); Zometa (Зомета); ***USA***: Reclast; Zometa; ***Venez.***: Zoldria; Zometa.